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Datasheet for the decision of 26 September 2023

Case Number: T 1345/20 - 3.3.08

Application Number: 12728976.7

Publication Number: 2718725

IPC: G01N33/92, G01N33/68

Language of the proceedings: EN

Title of invention:
METHOD FOR THE DIAGNOSIS OF GAUCHER'S DISEASE

Patent Proprietor:
Centogene GmbH

Opponent:
Sanofi

Headword:
Diagnosis of Gaucher's disease/CENTOGENE

Relevant legal provisions:
EPC Art. 100(b)

Keyword:
Grounds for opposition - insufficiency of disclosure (yes)

Decisions cited:
T 0298/17, T 0967/09, T 0063/06, T 0435/20

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1345/20 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 26 September 2023

Appellant: (Opponent)	Sanofi 54 Rue La Boétie 75008 Paris (FR)
Representative:	Garner, Stephen Robinson, Alexander Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Respondent: (Patent Proprietor)	Centogene GmbH Am Strande 7 18055 Rostock (DE)
Representative:	Bohmann, Armin K. Bohmann Anwaltssozietät Nymphenburger Straße 1 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 March 2020 rejecting the opposition filed against European patent No. 2718725 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Pilat
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 2 718 725, based on European patent application No. 12 728 976.7, was opposed on the grounds of Article 100(a) EPC, in conjunction with Articles 54 and 56 EPC, and of Article 100(b) EPC. The opposition division rejected the opposition.

II. The opponent (appellant) lodged an appeal requesting that the decision under appeal be set aside and the patent be revoked in its entirety.

III. The patent proprietor (respondent) replied to the appeal, initially requesting that the appeal be dismissed (main request) or, alternatively, that the patent be maintained in amended form based on any of auxiliary requests 1 to 5, all filed with the reply to the appeal.

IV. In a communication under Article 15(1) RPBA, the parties were informed of the board's provisional opinion on the issues of the case.

V. Both parties replied to the board's communication. With letter dated 24 September 2023, the respondent replaced the auxiliary requests on file by new auxiliary requests 2 to 13; as auxiliary request 1 the respondent requested not to allow the late-filed and new ground of opposition according to Article 100(c) EPC and Article 123(2) EPC into the proceedings, not to allow D18 into the proceedings, and to remit the case to the opposition division.

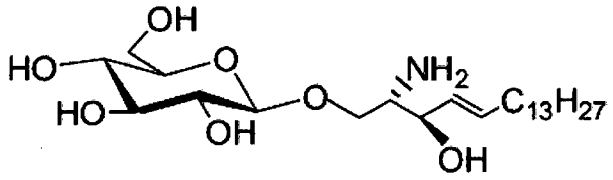
VI. Oral proceedings before the board of appeal took place on 26 September 2023. At the end of the oral

proceedings, the respondent maintained its main request but withdrew all auxiliary requests on file.

VII. Claims 1 and 4 of the main and sole request (claims as granted) read as follows:

"1. An in vitro method for diagnosing Gaucher's disease in a subject comprising:

detecting a biomarker in a sample from the subject, wherein the biomarker is free lyso-Gb1, wherein the sample is selected from the group comprising blood sample, serum sample, plasma sample and dry blood filter sample and wherein lyso-Gbl is of formula (I):



(I),

determining the level of the biomarker present in the sample,

comparing the level of the biomarker in the sample from the subject to a cut-off level, wherein if the level of the biomarker in the sample from the subject is higher than the cut-off level, this is indicative that the subject is suffering from or is at risk for developing Gaucher's disease and

wherein the cut-off level is 20 ng/ml if the sample is a blood sample and the cut-off level is 5.0 ng/ml if the sample is a serum sample or a plasma sample."

"4. The method according to any one of claims 1 to 3, wherein the biomarker and/or the at least one additional biomarker is detected by means of immunoassay, mass spectrometric analysis, biochip

array, functional nucleic acids and/or a fluorescent derivative of free lyso-Gb1."

VIII. The arguments of the appellant, insofar as relevant to the present decision, may be summarised as follows:

The patent explicitly envisaged the use of immunoassays as a means of detecting lyso-Gb1 (glucosylsphingosine) (granted claim 4, paragraphs [0036], [0089], [0112], and [0168]), but provided no information regarding the availability of antibodies suitable for an immunological assay, or on how the skilled person might obtain such antibodies. Lyso-Gb1 represented a challenging molecule as it lacked features commonly recognized to act as epitopes for antibody recognition. The skilled person would thus have to embark on a research programme to identify antibodies capable of recognising lyso-Gb1 as an antigen at low concentrations and discriminating lyso-Gb1 from similar molecules, such as e.g. glucosylceramide (GlcCer or Gb1) or lyso-Gb3, which could be present in the sample at much higher concentrations. Even if antibodies for small antigenic molecule might exist (as stated in the appealed decision, section 20.3.2), this did not necessarily imply that the design of an antibody for other small target molecule was a matter of routine.

IX. The arguments of the respondent, insofar as relevant to the present decision, may be summarised as follows:

Since the generation of antibodies binding to known targets was a matter of routine (T 431/96, Guidelines for Examination in the European Patent Office March 2023, G-II.5.6.2), so was the development of an immunoassay for the detection of a given target. There was no evidence showing that the above assumptions were

incorrect and that there was a technical prejudice so that the skilled person was unable to generate antibodies against free lyso-Gb1. According to T 63/06, there was a legal presumption of validity once a patent was granted and it was the opponent who had the burden of proof to demonstrate that the claimed invention did not work. Serious doubts demonstrated by verifiable facts had to be put forward by the opponent (T 298/17 and T 967/09), but the opponent had only made mere statements that free lyso-Gb1 was a difficult target, without presenting evidence therefor. The conclusions of T 435/20 did not apply to the present case because it was related to different kinds of antigens, namely non-contiguous epitopes of a protein.

X. The final requests of the appellant were to set aside the decision under appeal and to revoke the patent.

The final request of the respondent was to dismiss the appeal.

Reasons for the Decision

Main Request (claims as granted)

Article 100(b) EPC

1. Claim 1 of the main request is directed to an vitro method for diagnosing Gaucher's disease comprising detecting free lyso-Gb1 in a sample from a subject. Dependent claim 4 further defines the means of detection as being immunoassay, mass spectrometric analysis, biochip array, etc (for the full wording of the claims, see section VII. above). Hence claim 4 explicitly encompasses immunoassays as means of detection of free lyso-Gb1, to be used for the purpose

of claim 1, i.e. for the diagnosis of Gaucher's disease. Accordingly, the enablement of the claimed method requires that immunoassays for detection of free lyso-Gb1 are sufficiently disclosed in the patent.

2. It is undisputed that neither the patent nor the prior art discloses how to generate and obtain an antibody or fragment thereof capable of detecting free lyso-Gb1, let alone at a concentration of 20 ng/ml or 5 ng/ml in blood or serum samples, respectively, which is capable of discriminating free lyso-Gb1 from glucosylceramide (GlcCer or Gb1) or from lyso-Gb3 in said samples, so as to enable the skilled person to perform immunoassays capable of diagnosing Gaucher's disease.

3. While the provision of antibodies against known targets is usually a matter of routine, as argued by the respondent and supported by case law (e.g. T 431/96), this is only the case if the skilled person knows from the disclosure in the patent or from common general knowledge (i) which antigens are suitable for raising antibodies having the desired properties and (ii) which screening process should be used to select these antibodies without undue burden (see decision T 435/20, reasons 28). The fact that the case underlying T 435/20 is related to non-contiguous epitopes of a protein rather than to small non-peptidic target molecules like in the present case (see below) does not disqualify the above mentioned conclusions which are generally applicable to any antigen. The overall rationale and teaching of T 435/20 is that raising and screening of antibodies is routine for an unconventional target antigen only if both the antigen for raising the desired antibodies and the process for selecting them are known.

4. The target molecule in the present case, glucosylsphingosine or lyso-Gb1, is a small molecule comprising a single hexose ring joined to a short (C13) lipid tail. It thus represents an especially challenging target for the design of a suitable antibody as it lacks features which are known to be suitable epitopes for antibody recognition, such as polypeptide or polysaccharide moieties. Hence it can be considered an unconventional target in the sense of decision T 435/20. There is no indication, either in the prior art or in the patent whether glucosylsphingosine is a suitable antigen, but even if it were, there is still no teaching which screening process would ensure a reliable selection of antibodies specifically detecting only free lyso-Gb1 at low concentration, knowing that there are many other structurally related small molecules, which could even be present at higher concentration in the sample from the subject to be diagnosed. Accordingly, the two criteria of T 435/20 (supra) for enablement of antibodies against an unconventional target are not fulfilled.

5. It is true, as argued by the respondent, that there is a legal presumption of validity once a patent is granted (T 63/06) and that the opponent bears the burden of proof when arguing that the claimed subject-matter is insufficiently disclosed (T 298/17, reasons 2.8). The patent contains no experimental evidence and/or information on how to obtain the above antibodies. It is therefore enough for the appellant to establish a lack of sufficiency of disclosure by merely raising serious doubts, e.g. by comprehensive and plausible arguments that the common general knowledge and the patent provide insufficient information to reliably obtain an anti-lyso-Gb1 necessary for the immunoassay

of claim 4 (see T 63/06, headnotes, reasons point 3.3.1; Case law of the Boards of Appeal, 10th edition 2022, hereinafter "Case Law", III.G.5.2.2 c)). In such a case, it cannot be expected that the appellant has to prove that a claimed immunoassay cannot be performed, which would be tantamount to providing negative evidence, i.e. that no specific discriminating antibodies can be obtained. Serious doubts substantiated by verifiable facts (T 967/09, reasons 6.) are thus not necessary to establish a lack of sufficiency in the present case; it is enough that serious doubts are raised in the form of comprehensible and plausible arguments (T 63/06, reasons 3.3.2). Moreover, it is not required to prove that carrying out the invention is inherently impossible, but only to provide arguments casting doubt on whether the claimed immunoassay for free lyso-Gb1 can be carried out on the basis of the patent specification and common general knowledge without requiring significant experimentation and the exercise of inventive skill (Case Law, II.C. 9.4). Hence the appellant's reasoned arguments reverse the burden of proof, so that it would then be for the respondent to prove that the skilled person could have performed the immunoassay without undue burden.

6. Under these circumstances and without the respondent having provided evidence to the contrary, the board considers that the appellant plausibly argued that common general knowledge would not enable the skilled person to put this feature into practice.

7. In this context, the board notes that the respondent's arguments based on the Guidelines for Examination in the European Patent Office March 2023, section G-II 5.6.2, are not persuasive either. Not only are the Guidelines for Examination not binding for the boards,

but also the conclusions in the cited section are actually not applicable to the present case, as they only address how an inventive step is to be assessed for "a novel, further antibody binding to a known antigen". As explained above, this is not the case here. While the immunoassay in claim 4 involves the use of an antibody specifically binding to a known small target molecule, no such antibodies were available on the relevant date of the patent nor was the target molecule known to be an antigen at all.

8. Finally, as to the respondent's arguments, based on the statement in section 20.3.2 of the appealed decision, that antibodies for small molecule antigens – and particularly for lipids – existed in the prior art, the board notes that not only there is no evidence on file supporting this statement but, most importantly, no such antibody was deemed representative of the antibodies to be identified. The respondent has not explained how this knowledge would be of use to the skilled person when attempting to obtain antibodies to the particular small target molecule of the claimed method.

9. The board thus disagrees with the conclusions of the opposition division on section 20.3.2 of the appealed decision and comes to the conclusion that the claims of the main request are not sufficiently disclosed. Hence the ground for opposition under Article 100(b) EPC prejudices the maintenance of the patent as granted.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated