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Datasheet for the decision of 30 July 2019

Case Number: T 1704/15 - 3.3.07

Application Number: 08715795.4

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Language of the proceedings: EN

Title of invention:
RECEPTOR AND ANTIGEN TARGETED PRODRUG

Applicant:
Vergell Medical S.A.

Headword:
Prodrug / VERGELL

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main and auxiliary request (no)

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Case Number: T 1704/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 30 July 2019

Appellant: (Applicant)	Vergell Medical S.A. 5, Rue de l'Evêché 1204 Geneva (CH)
Representative:	Müller-Boré & Partner Patentanwälte PartG mbB Friedenheimer Brücke 21 80639 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 23 March 2015 refusing European patent application No. 08715795.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	S. Albrecht
	Y. Podbielski

Summary of Facts and Submissions

I. The appeal of the applicant (appellant) lies from the decision of the examining division to refuse European patent application No. 08715795.4, published as WO 2008/098788.

II. The decision of the examining division was based on a single request filed with letter of 3 February 2015 (hereinafter "main request").

Claim 1 of this request read as follows:

"1. A prodrug, comprising
(i) at least one pharmaceutically and/or diagnostically active compound,
(ii) at least one receptor and/or antigen targeting moiety,
(iii) at least one cleavable linker, and
(iv) a protein-binding moiety,
wherein the first pharmaceutically and/or diagnostically active compound is bound to the at least one cleavable linker,
wherein the receptor and/or antigen targeting moiety comprises a Gal- and/or GalNAc-cluster,
wherein the protein-binding moiety binds *in situ* to cysteine-34 of albumin and is selected from the group consisting of a maleinimide group, a halogenacetamide group, a halogenacetate group, a pyridylthio group, a vinylcarbonyl group, an aziridin group, a disulfide group, a substituted or unsubstituted acetylene group, and a hydroxysuccinimide ester group, and
wherein the first pharmaceutically and/or diagnostically active compound is a cytostatic agent."

III. The following documents were among those cited in the first instance examination proceedings:

D17: Macromolecular Bioscience, 1(8), 2001, pages 355-363
D44: WO 2006/092230

IV. In its decision the examining division considered document D44 to represent an equally valid starting point to document D17 for assessing inventive step of the main request. The claimed prodrugs differed from D44 in that they comprised at least one receptor and/or antigen targeting moiety comprising a Gal- and/or GalNAc-cluster. In the absence of any experimentally established surprising technical effect linked to this difference, the objective technical problem was the provision of alternative compounds. The solution proposed by the claimed subject-matter was obvious in the light of the teaching of D17. Accordingly, the claimed subject-matter was not inventive.

V. With the statement setting out the grounds of appeal, the appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of

(a) a main request submitted with the statement setting out the grounds of appeal filed with letter of 22 July 2015,

(b) or, as an auxiliary measure, on the basis of a single auxiliary request filed with the same letter.

The main request corresponded to the main request underlying the impugned decision.

VI. In a communication pursuant to Article 15(1) RPBA issued on 24 May 2019, the Board expressed its preliminary opinion that the subject-matter of claim 1 of the main request was obvious in the light of D17 as the closest prior art document taken in combination with D44.

The Board furthermore indicated that the same observations applied to the subject-matter of claim 1 of the auxiliary request.

VII. With letter of 4 July 2019, the appellant informed the Board that it would not attend the oral proceedings appointed for 8 July 2019 and requested a decision according to the state of the file.

VIII. With telefax of 8 July 2019 the Board notified the appellant that oral proceedings had been cancelled.

IX. The appellant's arguments presented in writing can be summarised as follows:

Document D17 was the closest prior art for the assessment of inventive step. This document disclosed prodrugs comprising a cytostatic agent, polyethylene glycol as a carrier and galactose units for active targeting. The prodrugs defined in the main request differed from those described in D17 in that they comprised a protein-binding moiety capable of binding in situ to cysteine-34 of albumin. The technical effect linked to this difference was the covalent binding of the claimed product to cysteine-34 of albumin in situ (e.g. after parenteral injection of the product to a subject), by means of which a macromolecular drug conjugate was formed. Apart from having an enhanced half-life and a reduced systemic toxicity this

conjugate also exhibited an enhanced passive transport to the desired site of action. The technical problem was therefore the provision of a prodrug which effectively combined passive and active targeting of cells possessing sugar receptors. The solution, i.e. a prodrug in accordance with claim 1 of the main request, was not rendered obvious in the light of the prior art documents on file. In particular, the skilled person faced with this technical problem would not have had any motivation to consult document D44 in the first place, as this document was directed to an entirely different purpose. Furthermore, D44 lacked any hint or incentive to isolate the protein moiety from the prodrugs described therein and to introduce it in the prodrugs of D17. The main request was therefore inventive.

For the same reasons, auxiliary request 1 also involved an inventive step.

X. The appellant had requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of a main request or alternatively on the basis of a single auxiliary request, both submitted with the statement setting out the grounds of appeal of 22 July 2015.

Reasons for the Decision

1. Main request - Article 56 EPC - claim 1

1.1 The closest prior art

1.1.1 In agreement with the appellant, the Board considers D17 as a suitable starting point for assessing inventive step of the claimed subject-matter.

D17 relates to a macromolecular prodrug comprising the anti-tumour agent cisplatin, polyethylene glycol (PEG) and a Gal-cluster as receptor and/or antigen targeting moiety. The PEG acts as a macromolecular carrier of the active agent prolonging its in vivo half-life and reducing its side effects (see page 355, columns 1 and 2). As regards the Gal-cluster, this moiety effectively binds to saccharide receptors such as the asialoglycoprotein receptors of HepG2 human hepatoma cells, and thereby provides for an active and specific targeting of these tumour cells (see in particular the abstract; page 356, column 1, second full paragraph and page 362, column 2, first full paragraph). In consequence, the tumour cells are enriched with the drug conjugate.

1.1.2 The Board also agrees with the appellant that the prodrug of claim 1 differs from the prodrugs described in D17 in that it comprises a protein-binding moiety which binds in situ to cysteine-34 of albumin and which is selected from the specific groups listed in claim 1.

1.2 Objective technical problem and solution

1.2.1 As a next step, the technical effect(s) linked to the aforementioned distinguishing feature need to be determined. In this regard the appellant identified several effects (see point IX. above). The Board considers these credible in the light of the prior art (see in particular page 9, first full paragraph of D44; page 355, column 1 of D17 and page 1, ultimate paragraph of the patent application as filed).

1.2.2 Accordingly, the objective technical problem to be solved by the claimed invention vis-à-vis D17 is the provision of a macromolecular prodrug which allows for

a higher amount of drug conjugate to reach the desired site of action, i.e. a tumour having galactose-binding receptors on the surface of its cells.

As a solution to this problem, a prodrug in accordance with claim 1 is provided.

1.3 Obviousness

1.3.1 Document D44 is directed to prodrugs which release a cytostatic agent (i.e. camptothecin or derivatives thereof) in tumour tissue (see page 1, lines 26 to 27). D44 thus belongs to the same technical field as D17 and the claimed invention.

More particularly, the prodrugs described in D44 comprise the following components:

(i) the cytostatic agent camptothecin bound to a cleavable linker and

(ii) a protein-binding moiety,

wherein the latter is preferably a maleinimide group and binds in situ to cysteine-34 of serum albumin (see claim 3 and page 9, first full paragraph).

Once this bond has been formed, the albumin takes up the role of endogenous carrier of camptothecin and allows for an enhanced uptake of this agent in tumour tissue, i.e. it achieves a passive targeting effect (see page 9, first full paragraph of D44; page 1, ultimate paragraph of the patent application as filed).

D44 thus pursues the same overall objective as D17, namely to increase the amount of a cytostatic agent

present within the tumour tissue. Accordingly, in the Board's judgement, the skilled person will be motivated to consult D44 in order to find a solution to the above mentioned technical problem.

From this document the skilled person not only learns that the aforementioned objective can be achieved by means of the endogenous carriers described therein (as described above), but also that these carriers have the advantage over synthetic polymeric carrier systems such as PEG of being chemically clearly defined (see page 9, second full paragraph in conjunction with page 1, paragraph 2 of D44). The skilled person thus infers from D44 that endogenous, albumin-based prodrug carriers are to be preferred over exogenous synthetic carriers such as PEG. Against this background, the skilled person will be motivated to replace the PEG carrier of the prodrug of D17 by the protein-binding moiety disclosed in D44, in order to solve the technical problem as posed, and will thereby arrive at the claimed invention in an obvious manner.

1.3.2 In the appellant's view, the skilled person in search of a solution to the above mentioned technical problem would not be motivated to introduce a protein-binding moiety into the prodrugs described in D17, the reasons being as follows:

(a) D17 already promoted that the active targeting achieved through the galactose residues was sufficient and effective in order to transport the anti-tumour drug to the desired site of action (hereinafter "argument (a)").

(b) The prodrugs of D17 already included a moiety acting as a carrier (i.e. PEG). Hence, the skilled

person would not have any incentive to provide these prodrugs with a further, supplementary carrier such as the protein-binding moiety disclosed in D44 (hereinafter "argument (b)").

1.3.3 With respect to argument (a), the Board notes that the appellant has not indicated any passage in D17 in support of its allegation. In the absence thereof this argument is not found convincing.

As for argument (b), this cannot succeed either in view of the fact that D44 provides the skilled person with a clear motivation to **replace** the synthetic PEG carrier with the protein-bind moiety.

1.3.4 The Board therefore concludes that claim 1 does not fulfil the requirements of Article 56 EPC.

2. Auxiliary request

This request solely differs from the main request in that the hydroxysuccinimide ester group has been deleted from the list of protein-binding moieties of claim 1. Accordingly, claim 1 of this auxiliary request does not fulfil the requirements of Article 56 EPC for the same reasons as claim 1 of the main request.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

K. Götz-Wein J. Riolo

Decision electronically authenticated