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Datasheet for the decision of 9 October 2014

Case Number: T 0569/11 - 3.3.07

Application Number: 01910775.4

Publication Number: 1263472

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Language of the proceedings: EN

Title of invention:
MODIFICATION OF BIOPOLYMERS FOR IMPROVED DRUG DELIVERY

Applicant:
GENZYME CORPORATION

Headword:

Relevant legal provisions:
RPBA Art. 15
EPC Art. 56

Keyword:
Oral proceedings - postponement (no)
Inventive step - main request (no) - auxiliary request (no)

Decisions cited:
T 1610/08

Catchword:

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Case Number: T 0569/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 October 2014

Appellant: (Applicant)	GENZYME CORPORATION One Kendall Square Cambridge, Massachusetts 02139-1562 (US)
Representative:	Wallace, Sheila Jane Marks & Clerk LLP 90 Long Acre London WC2E 9RA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 20 September 2010 refusing European patent application No. 01910775.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	D. T. Keeling

Summary of Facts and Submissions

I. The appeal of the applicant (appellant) lies from the decision of the examining division announced at the oral proceedings on 3 September 2010 refusing European patent application No. 01 910 775.4.

II. The documents cited during the examination proceedings included the following:

D4: WO 98/52614
D8: Bioconjugate Chem., 1999, 10, 755-763
D10: Journal of Controlled Release, 1998, 53, 93-103
D11: Bioconjugate Chem., 1998, 9, 749-757

III. The appealed decision was based on two sets of claims filed with letter of 2 August 2010 as main request and auxiliary request 1.

Claim 1 of both requests read as follows:

"1. A biologically active conjugate of a polyanionic polysaccharide and a therapeutic agent comprising a compound of formula:

G-C(O)-R-L-S-S-B

or a pharmaceutically acceptable salt thereof, wherein G-C(O)- is a polyanionic polysaccharide comprising at least one carbonyl group, -C(O)-, on the polysaccharide backbone bound to R, and R is an amino group or an oxygen atom, or a compound of formula:

G-C-R-L-S-S-B

or a pharmaceutically acceptable salt thereof,

wherein G-C- is a polyanionic polysaccharide having a methylene group, C, bound to R, and R is an imino or amino group, and wherein L is an ethyl spacer, B is a therapeutic agent, and each S is a sulfur atom.

IV. As far as inventive step is concerned, the decision of the examining division can be summarised as follows:

a) Any of D8 or D10 could be regarded as the closest prior art for both requests, because each of these documents disclosed a conjugate comprising a polyanionic polysaccharide and a therapeutic agent linked to each other via a cleavable ester bond. The problem to be solved was to be seen in "the provision of an alternative cleavable bond". The applicant did not provide any evidence for an unexpected effects of the claimed conjugates. The solution proposed in both requests to replace the ester bond with a disulfide bond was obvious in view of the teaching of D4. Moreover, the use of disulfide linkers was disclosed also in D11. Accordingly, the subject-matter of the main request and of the auxiliary request did not comply with the requirements of Article 56 EPC.

b) Following an alternative approach for the assessment of inventive step, D11 was the closest prior art. The technical problem was formulated as the provision of an alternative polymer carrier. The solution of the applicant to use a polyanionic polysaccharide such as hyaluronic acid was suggested by D8 and D10. Thus, the subject-matter of the main request and of the auxiliary request was obvious also also following this alternative approach.

V. The appellant lodged an appeal against that decision. With the statement setting out the grounds of appeal sent on 31 January 2011, the appellant sent two set of claims as main request and auxiliary request which were identical to the requests refused by the examining division.

VI. With letter dated 24 February 2014 the Board summoned the appellant to oral proceedings to be held on 9 October 2014.

VII. On 14 May 2014 the Board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Board of Appeal (RPBA; OJ EPO 2007, 536). In this communication, the Board informed the appellant that with regard to the assessment of inventive step it considered that the closest prior art was represented by document D11, in conformity with the second approach followed by the examining division. The other relevant documents to be considered in the discussion on the obviousness of the invention were D8 and D10.

VIII. With letter sent by fax on 8 October 2014, the appellant's representative informed the Board that she would not attend the oral proceedings. Furthermore, she stated that she had discovered from the European patent register that the Board had issued a communication on 14 May 2014. Said communication was however not received by the appellant's representative.

In the same letter of 8 October 2014 the appellant formulated the following requests:

a) To postpone the oral proceedings scheduled for 9 October 2014 to allow time for the appellant to

respond to the points raised in the Board's communication of 14 May 2014,

b) If postponement were not possible, to allow the appellant to file further written submissions that same day so that these could be considered during the oral proceedings.

IX. The registrar of the Board telephoned the appellant's representative on 8 October 2014 to inform her that she could file written submissions to be considered during oral proceedings, as requested in the letter sent on the same date.

X. Oral proceedings were held on 9 October 2014 in the absence of the appellant. The proceedings were interrupted at 9:20 so that the Board could establish whether the appellant had filed any further written submission by fax. The proceedings were resumed at 15:00. The Board noted that no fax had been received from the appellant's representative (see Minutes of the oral proceedings, last paragraph of page 2 and first paragraph of page 3). The Board then deliberated with regard to the issue of inventive step and at the end of the oral proceedings decided on the case.

XI. As far as they are relevant to the present decision, the arguments submitted by the appellant with regard to the requirements of Article 56 EPC can be summarised as follows:

Document D11 was not relevant for the assessment of inventive step. This document was only directed toward the modification of N-(2-hydroxypropyl)methacrylamide-(HPMA) which is a synthetic polymer that bore no structural resemblance to the polymers of the invention. The present invention was directed toward

enhancing the stability of a therapeutic agent by the modification of a polyanionic polysaccharide carrier polymer. Therefore, the lack of inventive step finding based on D11 as the closest prior art was ill-founded. Even if document D11 were regarded as the closest state of the art, the skilled person would not have been led to the compounds of the invention because there was no disclosure in this document that would have provided the motivation to change the carrier polymers. Furthermore, the entire disclosures of documents D8 and D10 were directed to hyaluronic acid conjugates with specific linkers. The polymers and linkers used in these documents were different from those disclosed in document D11. There was no disclosure in either of these documents that would have motivated the skilled person to modify the conjugates of document D11. Contrary to the appealed decision, the compounds of the present invention did present an inventive step over the compounds of the prior art.

XII. The appellant requested in writing to set aside the decision under appeal and to remit European patent application No 01910775.4 to the Examining Division for acceptance on the basis of the main request attached to the grounds of appeal. In the alternative, the appellant requested to set aside the decision under appeal and to remit the application to the Examining Division for acceptance on the basis of the claims of the auxiliary request attached to the grounds of appeal.

XIII. On 13 October 2014 the Board received from the appellant's representative a letter sent by fax. The fax was apparently sent on 8 October 2014 and received at the EPO on the same date ("EMPFANGZEIT 8.OKT. 23:01"). It was however printed only on 13 October 2014

("AUSDRUCKZEIT 13.OKT 7:05") and forwarded to the Board on that date.

The content of this letter could not be taken into account in that the Board became aware of it only when the decision was already adopted.

Reasons for the Decision

Procedural aspects

1. The appellant's representative sent, by fax and by online filing, on 8 October 2014, i.e. the day before the oral proceedings, a letter in which she stated that she had been instructed not to attend the oral proceedings. In the same letter she explained that whilst she was looking at the online European register in order to check the fax number to which the letter was to be sent, she discovered that the Board issued on 14 May 2014 a communication pursuant to Rule 15 of the Rules of Procedure of the Boards of Appeal (RPBA) which was never received by the appellant. As a consequence of this fact, she requested to postpone the oral proceedings or in the alternative to be allowed to file further submissions on the same day to be considered by the Board during the oral proceedings.

These requests are considered in the following sections.

1.1 *Request of postponement of the oral proceedings*

1.1.1 As a preliminary remark, the Board notes that the causes for the unsuccessful receipt of the communication of 14 May 2014 are not clear. In particular, from a check with the registry of the

Board, there appears to be no indication that an error internal to the EPO has occurred with the processing of the communication.

1.1.2 Independently from the above consideration, it is observed that there is no obligation for the Board to issue a communication under Rule 15 RPBA. The wording of the Rule itself makes it clear that the Board may send such a communication, but is not obliged to. Furthermore, if the Board decides to issue a communication, there are no time limits prescribed by Rule 15 RPBA.

From the above it is concluded that the fact that the appellant became aware of the communication shortly before the oral proceedings, is not *per se* a reason that obliges the Board to postpone the proceedings.

1.1.3 It is nevertheless necessary to verify whether in the light of the content of the communication, a postponement should be made in order to allow time for the appellant to react to the comments made by the Board. This requires an analysis of the points covered in the communication which is made in the next paragraph.

1.1.4 The first part of the communication contains a summary of the appealed decision and of the appellant's requests. The second part deals with the points that the Board intended to discuss at the oral proceedings. The only issue at stake is inventive step.

The Board provides its comments with regard to the two alternative approaches followed by the examining division for the assessment of inventive step and concludes that the second approach, starting from

document D11 as the closest prior art, appears to be the most appropriate. It is furthermore observed that the description does not contain any data supporting the presence of any particular effect or properties of the claimed conjugates that could be taken into account in the formulation of the technical problem. As to the obviousness of the solution, the Board indicates that this should be discussed taking into account the teaching of the closest prior art in combination with the teaching of documents D8 and D10.

1.1.5 The Board's communication does not include therefore any new objection or any new evidence in comparison with the decision of the examining division. Furthermore, the considerations made by the Board as to the assessment of inventive step are based on the second of the two approaches followed by the examining division in its decision (see point IV-b) above). In this respect, it is also noted that in the statement of the grounds of appeal the appellant already addressed the objection under Article 56 based on document D11 as closest prior art (page 7, paragraph "*Claim 1 - D11 as the closest prior art*").

1.1.6 In the light of the above, the Board estimates that despite the late receipt of the communication, it was still possible for the appellant to reply to the communication before the oral proceedings if it wished to do so, because it was already aware of the facts and arguments upon which the assessment of inventive step was based. In this context it is also observed that the case does not appear to involve any particular technical or legal difficulty. The fact that in the fax of 8 October 2014 the appellant's representative asked the Board, as an auxiliary request, to allow the filing of further submissions to be considered during the oral

proceedings, appears to confirm the above considerations as to the absence of any particular difficulty in dealing with the case.

1.1.7 The late discovery of the communication was certainly an unfortunate event for the appellant. However, according to Article 15(2) RPBA, the discretionary power of the Board to allow a change of date for oral proceedings has an exceptional character, i.e. only extraordinary circumstances can justify such a change (see T1610/08, point 3 of the Reasons). For the reasons given above, in the present case it was still possible for the appellant to cope with the cause underlying its request for postponement of oral proceedings, namely. the late discovery of the communication. Accordingly, in the Board's opinion the facts of the present case do not constitute an extraordinary circumstance that would justify a postponement of the date of oral proceedings.

2. *Request to have the possibility of filing new submissions to be taken into account during oral proceedings*

The decision to file new submissions at a late stage of the proceedings is a matter which is entirely the responsibility of the appellant. The Board then decides on the admissibility of these submissions in the light of Articles 12(4), 13(1) and 13(3) of the Rules of Procedure of the Board of Appeal. The appellant's representative was informed by the Registrar of the Board accordingly (see minutes of the phone conversation).

Main request and auxiliary request

Inventive step

3. The invention relates to biologically active conjugate-compounds useful for the *in vivo* delivery of therapeutic agents to specific cells, organs or tissues in a subject (see page 1, lines 1 to 13 and page 4 lines 1 to 8).

The conjugates-compounds defined in claim 1 are characterized by the presence of a polyanionic saccharide G linked to a therapeutic agent B by a linking moiety containing a disulfide bond (see claim 1). The therapeutic agent should contain a reactive thiol group or it should be modified in order to contain such a group which is required for the formation of the disulfide bond (page 6, lines 5-8 and page 8, lines 5-9).

4. *Closest prior art*

4.1 Documents D8, D10 and D11 relate to the same field as the present application in that they address the problem of delivering active substances by the use of conjugates-compounds, in which said substances are linked through a spacer group to a carrier.

4.2 The conjugate-compound disclosed in document D8 (see figure 2) is a hyaluronic acid-taxol bioconjugate, i.e. a compound in which the active agent taxol is linked to a hyaluronic acid moiety. Hyaluronic acid is one of the preferred polyanionic polysaccharide of the present application (see page 5, lines 3 to 15). This part of the conjugate corresponds therefore to the group G of claim 1. The moiety linking the hyaluronic acid part to

the taxol is an hydrazide-based radical which does not contain any disulfide group. Furthermore, taxol is a compound that does not contain any thiol group. Hence, the conjugate-compounds claimed in the present application differ from the compound disclosed in document D8 on account of the linking moiety and of the therapeutic agent.

4.3 The conjugate-compound disclosed in D10 is structurally similar to the compound of D8 in that it is constituted by a hyaluronic acid moiety linked through a hydrazide-based radical to an active ingredient which is hydrocortisone hemisuccinate, i.e. a molecule that does not contain any thiol group (figure 5). Hence, also in this case the distinguishing features of the conjugate-compounds of claim 1 are represented by the linking moiety and by the therapeutic agent.

4.4 Document D11 relates to the use of an (hydroxypropyl)methacrylamide-based polymer (HPMA-polymer) as a carrier for the delivery of water soluble drugs. The spacer group linking the HPMA-polymer to the drugs is a disulfide-based moiety which corresponds to the spacer group of present compounds of claim 1. In one of the two conjugate compounds specifically described in D11 the active agent contains a thiol radical (see pAnt-SH in Fig. 5). In the other conjugate (see RSS-OSH in Fig. 5) the active substance is reduced to produce a free thiol before the reaction with the polymeric portion (see page 753, right column, last paragraph). Thus, in both cases the therapeutic agent is substituted by a thiol group. Accordingly, the conjugates of D11 differ from the products of the current invention only on account of the carrier portion which is a HPMA-polymer while in present compounds the carrier is a polyanionic polysaccharide.

4.5 The above analysis shows that the conjugate-compounds disclosed in D11 are structurally closer than the products of documents D8 and D10 to the conjugates of the present application. Moreover, despite its synthetic nature, HPMA is described in D11 as a known carrier for the targeted delivery of drugs, exhibiting little immunogenicity. It qualifies therefore as a biopolymer according to the definition of the term biopolymer given on page 1 of the description of the application, i.e. a biocompatible polymer. The conjugate-compounds of D11 are furthermore expected to be stable in the bloodstream (see Introduction). The appellant's argument that a skilled person would not consider a document directed toward synthetic HPMA polymers, is therefore not convincing. In the Board's opinion the teaching of D11 suggests that the skilled person would consider also synthetic polymers such as HPMA as suitable moieties for transporting, delivering and stabilizing a drug.

In the light of the above, the Board considers in agreement with the second approach of the first instance decision, that document D11 represents the closest prior art for the assessment of inventive step.

5. *Technical problem*

5.1 According to the description, the problem addressed by the inventors was to provide chemically modified biopolymers for the delivery of therapeutic agents to specific tissues (page 1, lines 5-8). Said biopolymers should provide for improved stability of the therapeutic agents and improved targeting to specific tissues (page 6 line 25 to page 7 line 3).

5.2 The experimental part of the description provides information as to the preparation of the intermediate compounds and of the final conjugates. There are however no data concerning properties or effects of said conjugates. In particular, there appears to be no experimental support for the properties mentioned in the description such as an improved stability of the therapeutic agents or improved targeting to specific tissue.

5.3 Having regard to the above, the Board considers that the technical problem in the light of D11 is to be seen as the provision of an alternative biologically active conjugate-compound containing a disulfide linkage.

6. *Obviousness*

6.1 As discussed above, documents D8 and D10 disclose conjugate-compounds in which the carrier group is a hyaluronic acid moiety. It would be readily apparent to the skilled person that the hyaluronic acid, like the HPMA polymer, contains various carboxylic acid groups which can form a bond with the linking moiety of the conjugates of D11. In other words, he would recognise that hyaluronic acid could replace as carrier group the HPMA in the conjugates of D11 because it contains the same functional moieties that allow the formation of a bond with the disulfide-containing linker. Moreover, there is no indication in D8 or D11 that hyaluronic acid can be conjugated only to the specific active molecules considered in these documents. Quite to the contrary, the fact that in these two documents two different and unrelated active ingredients are conjugated to hyaluronic acid, suggests that the latter is a versatile carrier which can be used to transport and deliver various active substances.

6.2 In the light of the above, the Board considers that the skilled person faced with the mere problem of providing an alternative to the conjugate-compound of document D11, would easily conceive of replacing HPMA with any alternative carrier such as hyaluronic acid.

It follows that the conclusion of the examining division holds good and that the subject-matter of claim 1 does not comply with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Schneider J. Riolo

Decision electronically authenticated