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**Datasheet for the decision
of 19 March 2020**

Case Number: T 2428/17 - 3.3.07

Application Number: 04768450.1

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Language of the proceedings: EN

Title of invention:

DESIGN OF RE-TARGETED TOXIN CONJUGATES

Applicant:

Ipsen Bioinnovation Limited

Headword:

DESIGN OF RE-TARGETED TOXIN CONJUGATES/Ipsen Bioinnovation Limited

Relevant legal provisions:

EPC Art. 54, 53(c)

Keyword:

All requests - Novelty (No)
Exceptions to patentability - method for treatment by therapy
- Auxiliary requests 1 and 3



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Case Number: T 2428/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 March 2020

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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 20 June 2017
refusing European patent application No.
04768450.1 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman A. Usuelli
Members: D. Boulois
P. Schmitz

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division to refuse European patent application n° 04 768 450.1. The decision was based on 4 sets of claims filed with letter of 21 December 2016 as main request and auxiliary requests 1-3.
- II. The documents cited during the examination and appeal proceedings included the following:
- D7: WO 98/07864
D8: WO 94/21300
D9: EP 0 467 536
D16: WO 01/21213
- III. According to the decision under appeal, claims 1,2,6 and 7 of the main request were not novel *inter alia* over D7-D9 and D16:
- In D7, the targeting moiety was IGF-1, attached to LH(N) which, according to the definition of the present application, contained both the protease and the translocation domain.
 - In D8, claim 14 defined a conjugate, in which the targeting moiety was IGF-II, the protease was "the domain or domain fragment of the light chain of botulinum neurotoxin having Zn dependent metalloprotease activity" and the translocation domain was "the domain or domain fragment of the botulinum neurotoxin heavy chain responsible for translocation of the toxin across the cell membrane".
 - D9 disclosed in the examples one of the possible results as defined by the claimed method: in the TGF-alpha-Pseudomonas Exotoxin (PE40) prepared, TGF-alpha

was the targeting moiety and PE40 contained both the protease and the translocation domain.

- D16, conjugates were prepared which consisted of three domains: the first domain cleaved one or more proteins essential to exocytosis, the second domain translocated the first domain into the cell, and the third domain targeted the agent into an endocrine cell. All of the ligands selected for the third domain were known to increase secretion from the target cell.

Claims 1-4 of auxiliary request 1 were not novel over the same documents, and the claims of auxiliary request 1 were objectionable under Article 53(c) EPC.

The subject-matter of claims 1,2,6 and 7 of auxiliary request 2 was also not novel.

Claims 1-4 of auxiliary request 3 were also not novel over the same documents, and the claims of auxiliary request 3 were objectionable under Article 53(c) EPC.

IV. The patent applicant (hereinafter the appellant) filed an appeal against the decision. With the statement of grounds of appeal dated 3 October 2017, the appellant submitted a main request and auxiliary requests 1-3, identical to the requests on file in the examination proceedings.

Independent claims 1 and 2 of the main request read as follows:

"1. A method of preparing a non-cytotoxic toxin conjugate for the inhibition or reduction of secretion from a target cell, which method comprises:

(A) identifying an agonist that increases said secretion from said target cell upon binding of the

agonist to a receptor on said target cell wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell; and

selecting said agonist as a targeting moiety on the basis of its specific agonist properties; and

(B) preparing a non-cytotoxic protease conjugate, said conjugate comprising:

(i) an agonist targeting moiety identified by step (A), wherein said agonist binds the conjugate to a receptor on said target cell;

(ii) a non-cytotoxic protease or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(iii) a Translocation Domain that translocates the proteases or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell."

"2. A method of preparing a non-cytotoxic toxin conjugate for the inhibition or reduction of secretion from a target cell, which method comprises:

(A) identifying an agonist that increases said secretion from said target cell upon binding of the agonist to a receptor on said target cell wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell; and

selecting said agonist as a targeting moiety on the basis of its specific agonist properties; and

(B) preparing a non-cytotoxic protease conjugate, said conjugate comprising:

(i) an agonist targeting moiety identified by step (A), wherein said agonist binds the conjugate to a receptor on said target cell;

(ii) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof, which DNA sequence is

expressible in the target cell and when so expressed provides a protease or protease fragment capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(iii) a Translocation Domain that translocates the DNA sequence encoding the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.”.

The subject-matter of independent claims 1 and 2 of the auxiliary requests read as follows, the difference(s) compared with the main request shown in bold or struck through:

Auxiliary request 1

"1. Use of an agonist that increases secretion from a target cell upon binding of the agonist to a receptor on said target cell wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell as a Targeting Moiety component in a non-cytotoxic toxin conjugate for the inhibition or reduction of said secretion from said target cell, wherein said agonist targeting moiety is selected on the basis of its specific agonist properties, and wherein said conjugate further comprises:

(i) a non-cytotoxic protease or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(ii) a Translocation Domain that translocates the proteases or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.”

"2. Use of an agonist that increases secretion from a target cell upon binding of the agonist to a receptor on said target cell wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell

as a Targeting Moiety component in a non-cytotoxic protease conjugate for the inhibition or reduction of said secretion from said target cell, wherein said agonist targeting moiety is selected on the basis of its specific agonist properties, and wherein said conjugate further comprises:

(i) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof, which DNA sequence is expressible in the target cell and when so expressed provides a protease or protease fragment capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(ii) a Translocation Domain that translocates the DNA sequence encoding the proteases or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell."

Auxiliary request 2

"1. A method of preparing a non-cytotoxic toxin conjugate for the inhibition or reduction of **undesirable** secretion from a target cell, which method comprises:

(A) identifying an agonist that **stimulates increases an increase in said undesirable** said secretion from said target cell upon binding of the agonist to a receptor on said target cell, **wherein said undesirable secretion contributes to the symptoms associated with a medical condition or disease**, and wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell; and

selecting said agonist as a targeting moiety on the basis of its specific agonist properties; and
(B) preparing a non-cytotoxic protease conjugate, said conjugate comprising:
(i) an agonist targeting moiety identified by step (A), wherein said agonist binds the conjugate to a receptor on said target cell;
(ii) a non-cytotoxic protease or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and
(iii) a Translocation Domain that translocates the proteases or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell."

"2. A method of preparing a non-cytotoxic toxin conjugate for the inhibition or reduction of **undesirable** secretion from a target cell, which method comprises:

(A) identifying an agonist that **stimulates increases an increase in said undesirable** ~~said~~ secretion from said target cell upon binding of the agonist to a receptor on said target cell, **wherein said undesirable secretion contributes to the symptoms associated with a medical condition or disease, and** wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell; and
selecting said agonist as a targeting moiety on the basis of its specific agonist properties; and
(B) preparing a non-cytotoxic protease conjugate, said conjugate comprising:
(i) an agonist targeting moiety identified by step (A), wherein said agonist binds the conjugate to a receptor on said target cell;

(ii) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof, which DNA sequence is expressible in the target cell and when so expressed provides a protease or protease fragment capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and
(iii) a Translocation Domain that translocates the DNA sequence encoding the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.”.

Auxiliary request 3

"1. Use of an agonist that increases undesirable secretion from a target cell upon binding to a receptor on said target cell, wherein said undesirable secretion contributes to symptoms associated with a medical condition or disease, wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell as a Targeting Moiety component in a non-cytotoxic toxin conjugate for the inhibition or reduction of said secretion from said target cell, wherein said agonist targeting moiety is selected on the basis of its specific agonist properties, and wherein said conjugate further comprises:

(i) a non-cytotoxic protease or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and
(ii) a Translocation Domain that translocates the proteases or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.”.

"2. Use of an agonist that increases undesirable secretion from a target cell upon binding of the

agonist to a receptor on said target cell, wherein said undesirable secretion contributes to symptoms associated with a medical condition or disease, wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell as a Targeting Moiety component in a non-cytotoxic toxin conjugate for the inhibition or reduction of said secretion from said target cell, wherein said agonist targeting moiety is selected on the basis of its specific agonist properties, and wherein said conjugate further comprises:

(i) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof, which DNA sequence is expressible in the target cell and when so expressed provides a protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said target cell; and

(ii) a Translocation Domain that translocates the DNA sequence encoding the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the target cell.”.

V. A Board's communication dated 27 September 2019 was sent to the appellant. It stated in particular that none of the requests was novel over D7, D8 and D16. Moreover, the claims of auxiliary requests 1 and 3 were under the form of a use prohibited by Article 53(c) EPC.

VI. The appellant did not file any substantive reply to the Board's communication.

VII. With a letter dated 24 February 2020, the appellant informed the Board that it would not be attending the oral proceedings.

VIII. Oral proceedings planned for 16 March 2020 were cancelled.

IX. The arguments of the appellant may be summarized as follows:

The present claims did not relate to a new product. Instead, the applicant had developed a counter-intuitive method for selecting a targeting moiety (TM) for use in a therapeutic product to treat undesirable secretion from a target cell. The TM was based on its unwanted ability to stimulate said undesirable secretion from said target cell, which contributed to the symptoms of the medical condition or disease intended for treatment.

Main request - Novelty

The main request was novel over D7, since it did not disclose directly an unambiguously a method step of purposively identifying and selecting, based on its functionality, an agonist that stimulated an increase in undesirable secretion from a target cell. D7 was completely silent in this regard.

There was nothing in D8 which suggested the counter-intuitive selection of a TM because it had an agonist activity on the target cells. The TM used in D8 did not have an agonist effect as defined in the context of the present invention, on the target cells.

The explicit teaching of D16 was to select a TM based solely on its specificity and/or affinity for a target cell. Further, there was no disclosure of a method step of purposively identifying and selecting, based on its

functionality, an agonist that stimulated an increase in undesirable secretion from a target cell.

The main request was therefore novel.

Auxiliary request 1

There was no disclosure in any of the cited prior art of a use as set out in claim 1 of auxiliary request 1.

Auxiliary requests 2 and 3

The claims of these requests complied with Article 54 EPC for the same reasons as set out above for the main request.

X. Requests

The appellant (applicant) requests that the decision under appeal be set aside and a patent be granted on the basis of the set of claims of the main request, or alternatively on one of auxiliary requests 1-3, all filed with letter of 3 October 2017.

Reasons for the Decision

1. Main request - Novelty

- 1.1 The invention defined in independent claims 1 and 2 is in the form of two process claims for "preparing a non-cytotoxic toxin conjugate for the inhibition or reduction of secretion from a target cell".

The conjugate to be prepared comprises (i) an agonist targeting moiety identified and selected such as it increases a secretion from a target cell, (ii)

respectively a non-cytotoxic protease or fragment thereof (claim 1) or a DNA sequence encoding such protease or a fragment thereof (claim 2), and (iii) a translocation domain.

- 1.2 The Board observes that a manufacturing process for the preparation of a product does not become new simply by indicating or explaining a property of a product, possibly previously unknown or even unexpected in the art, or by the mere explanation of an effect, even if, as argued by the appellant in the present case, this effect would be counter intuitive, if this process is not different from other processes which are already known in the art.

Thus, in the present case, when assessing novelty, the purpose of "the inhibition or reduction of secretion from a target cell" process cannot limit the claimed process over the prior art. The wording of the process claims 1 and 2 has to be construed as concerning a method for preparing a conjugate "**suitable**" "for the inhibition or reduction of secretion from a target cell", and novelty has to be assessed with regard to the process steps present in claims 1 or 2, i.e. steps (A) and (B).

As regards said steps characterizing the claimed process, namely step (A) of identification of an agonist targeting moiety, and step (B) of preparation of the conjugate, they are very generally defined and are not characterized by further particular process features.

Step (A) is particularly undefined and encompasses even a simple identification of the agonist by literature

review, as mentioned in the description of the present application (see page 6 of the description of the patent application), or explicitly shown in example 25 of the present application wherein Epidermal Growth Factor is selected by such literature review.

Step (B) is also not characterized by any further preparation feature, but uniquely by the components of the conjugate which is to be prepared.

- 1.3 D7 discloses specifically the identification and selection of a targeting moiety, such as a tandem IgG binding domain, insulin-like growth factor-1 (IGF-1) and cholera toxin A subunit (see page 7-8 of D7). IGF-1 is known as an agonist of the receptor for insulin, said insulin being one of the preferred embodiments as agonist targeting moiety of the present application (Cf. examples 9 and 11 of the present application).

D7 discloses on pages 13 as well as on pages 16 and 20 a conjugate with IGF-1 as targeting moiety, attached to LH(N), namely respectively $2L_{fXa}/2H_{423}/A$ -IGF-1 and $L_{fXa}/3H_{423}/A$ -IGF-1 which, according to the definition of the present application (see application on page 13, last par.- page 14, first par.; see page 20 l. 4-26), contains both the protease and the translocation domain; the same function of protease and translocation is also disclosed and explained in D7 (see page 3, last par., page 4 2nd par., page 11, l. 1-4; page 11, last par.-page 12 first par.).

Example 1 of D7 discloses the further preparation of ligands made from these molecules and DNA sequences encoding a non-cytotoxic protease; said example mentions also that the ligand incorporates a specific

binding activity into the polypeptide (see page 20, lines 11 to 14).

Consequently, the subject-matter of claims 1 and 2 of the main request is not novel over D7

- 1.4 D8 discloses in example 6 and claims 14 and 16 the preparation of a conjugate by combining an insulin like growth factor II (IGF-II), a translocation domain, and a botulinum neurotoxin having a metalloprotease activity; IGF-II is known for stimulating the secretion of certain hormones, and for being inter alia an agonist of the receptor for insulin, which is one of the preferred embodiments of the present application. The agent is tested in example 6 for its ability to inhibit the insulin-stimulated increase in glucose, which shows that IGF-II was selectively chosen for its activity on specific receptors. Examples 1 and 6 show the preparation of a ligand of IGF-I and botulinum neurotoxin-B with a translocation domain.

Consequently, the subject-matter of at least claim 1 of the main request is not novel over D8.

- 1.5 D16 describes the covalent binding of a hybrid of two clostridial neurotoxins, in which the Hc region has been removed, to a targeting moiety and a L-chain containing an endopeptidase activity (see page 7, last par. - page 8, 2nd par.; see -page 4th par. - page 17, 2nd par.). The targeting moiety can be an agonist as defined in present application, such as insulin (see D16, page 12). This disclosure is confirmed by claims 1-5 of D16.

Consequently, the subject-matter of at least claim 1 of the main request is not novel over D16.

1.6 The main request does not meet the requirements of Article 54 EPC.

2. Auxiliary request 1 - Novelty and Article 53(c) EPC

2.1 The subject-matter of claims 1 and 2 has been reformulated as the use of "an agonist that increases secretion from a target cell upon binding of the agonist to a receptor on said target cell wherein said receptor undergoes endocytosis to be incorporated into an endosome within said target cell", as a "targeting moiety ... for the inhibition or reduction of said secretion from said target cell".

2.2 This use is explicitly disclosed in D16, which mentions that the conjugate disclosed therein is capable of inhibiting the secretion of the target cell (see page 7, last par.-page 8 first par.; claims 1-5 , 6 and 25).

Moreover, document D8 shows also in example 6 the inhibition of the insulin stimulated increase in glucose transporter expression by a conjugate comprising IGF-II coupled with a protease and a translocation domain.

2.3 Consequently the subject-matter of at least claim 1 of auxiliary request 1 is not novel.

2.4 Claims 1 and 2 relate to the use of a conjugate to inhibit or reducing a secretion from a target cell. As explained in the description of the application, hypersecretion may be associated to several pathological conditions (page 4, lines 25 to 35). Thus, inhibiting or reducing the secretion qualifies as a method of treatment by therapy. Thus, claims 1 and 2 of

auxiliary request 1 do not comply with the requirements of Article 53(c) EPC.

3. Auxiliary request 2 - Novelty

3.1 In comparison to the main request, claims 1 and 2 of this request relate now to the inhibition or reduction of "undesirable secretion" and have been amended by following features in the claimed step (A):
"identifying an agonist that **stimulates increases an increase in said undesirable** said secretion from said target cell upon binding of the agonist to a receptor on said target cell, **wherein said undesirable secretion contributes to the symptoms associated with a medical condition or disease"**.

3.2 It is not clear what is meant by an "undesirable secretion", because this term has also a subjective meaning. For instance, a secretion linked with the use of insulin as agonist may indeed be desirable or undesirable according to the medical circumstances or conditions; this amendment does therefore not change the scope of claims 1 or 2.

3.3 Since the agonists identified in the disclosure of documents D7, D8 and D16 provide an effect of stimulation of secretion as claimed in step (A), the amendments have no impact on the assessment of novelty over said documents, and the conclusions are the same as for the main request.

3.4 Consequently, auxiliary request 2 does not meet the requirements of Article 54 EPC.

4. Auxiliary request 3 - Novelty and Article 53(c) EPC.

- 4.1 The subject-matter of claims 1 and 2 of auxiliary request 3 correspond to the subject-matter of the same claims of auxiliary request 1, with the same restrictions that had been introduced in claims 1 and 2 of auxiliary request 2.
- 4.2 As for auxiliary request 2, these amendments cannot have an incidence on the assessment of novelty over D8 and D16, which therefore remain relevant for novelty.
- 4.3 Consequently, auxiliary request 3 does not meet the requirements of Article 54 EPC.
- 4.4 Claims 1 and 2 of this auxiliary request do not comply with the requirements of Article 53(c) EPC for the same reasons as set out above for the subject-matter of claims 1 and 2 of auxiliary request 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



B. Atienza Vivancos

A. Uselli

Decision electronically authenticated