Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 6 October 2017

Case Number: T 0703/16 - 3.3.04

Application Number: 00964574.8

Publication Number: 1214351

IPC: C07K14/715

Language of the proceedings: EN

Title of invention:
Methods of screening for compounds that modulate the LSR-Leptin interaction and their use in the prevention and treatment of obesity-related diseases

Applicant:
Merck Serono Biodevelopment

Headword:
LSR-Leptin interaction/MERCK SERONO BIODEVELOPMENT

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
"Added subject-matter (yes)"

Decisions cited:
G 0003/89, G 0011/91, G 0002/10, T 0002/81, T 1063/96

Catchword:

-

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0703/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 October 2017

Appellant: (Applicant)	Merck Serono Biodevelopment 37, rue Saint-Romain 69008 Lyon (FR)
Representative:	Merck Serono SA Intellectual Property Zone Industrielle de l'Ouriettaz 1170 Aubonne (CH)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 13 October 2015 refusing European patent application No. 00964574.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	R. Morawetz
Members:	B. Claes
	L. Bühler

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application No. 00964574.8, published as international patent application WO 01/21647 (hereinafter "application as filed"), which has the title "*Methods of screening for compounds that modulate the LSR-Leptin interaction and their use in the prevention and treatment of obesity-related diseases*".

II. The examining division held that claim 1 of a main request and of an auxiliary request 1, both filed with a letter dated 2 October 2014, contained added subject-matter contrary to Article 123(2) EPC.

III. With its statement of grounds of appeal the appellant submitted a new main request and three auxiliary requests 1 to 3 and argued that the subject-matter of the claims of these requests met the requirements of Article 123(2) EPC.

IV. After having been summoned to oral proceedings, the appellant was informed, in a communication pursuant to Article 15(1) RPBA, *inter alia* of the board's preliminary opinion that, in relation to claim 1 of the main request and auxiliary request 1, the feature "*a sequence consisting of the amino acid residues 112 to 143 of a polypeptide sequence selected from the group consisting of SEQ ID NO: 32 or SEQ ID NO: 34*" had no basis in the application as filed as required by Article 123(2) EPC. The board therefore agreed with the decision of the examining division in this respect.

V. With a letter of 2 October 2017 the appellant filed a new main request and withdrew auxiliary requests 1 and 2 filed with the statement of grounds of appeal.

Claim 1 of the main request now read:

"1. A leptin polypeptide fragment that modulates an activity of the Lipolysis stimulated receptor (LSR), consisting of *a sequence consisting of the amino acid residues **112** to **143** of a polypeptide sequence selected from the group consisting of SEQ ID NO: 32 or SEQ ID NO: 34*" (emphasis added by the board).

VI. Oral proceedings before the board took place as scheduled. At the end of the oral proceedings the appellant maintained the main request and a sole auxiliary request, *i.e.* auxiliary request 1 newly filed during the oral proceedings.

Claim 1 of auxiliary request 1 read:

"1. A leptin polypeptide fragment that modulates an activity of the Lipolysis stimulated receptor (LSR), consisting of a sequence consisting of the amino acid residues **117** to **167** of a polypeptide sequence selected from the group consisting of SEQ ID NO: 32 or SEQ ID NO: 34" (emphasis added by the board).

At the end of the oral proceedings the Chairwoman announced the decision of the board.

VII.

VIII. The appellant's arguments can be summarised as follows:

Main request - claim 1

The invention was a leptin polypeptide fragment that modulated the activity of the lipolysis stimulated receptor (LSR), comprising 4 to 50 contiguous amino acids of a leptin polypeptide sequence shown in Figure 13 and containing the "*leptin fragment central sequence*" (see page 3, lines 19 to 24), the latter being QKPE for mice and ETLD for humans (see page 22, lines 20 to 21). Examples 7 and 8 of the application as filed demonstrated that a 22-amino-acid region of leptin containing the leptin fragment central sequence was sufficient to modulate the activity of LSR *in vitro* and *in vivo* in the same way as intact human leptin (see also page 3, lines 11 to 14 and 19 to 24).

The different leptin peptide sequences disclosed in the tables of example 10 were preferred embodiments of the invention (see page 22, lines 9 to 13, and pages 82 and 83). SEQ ID NOs 56 and 66 corresponded to the fragments "112-133" of human and mouse leptin respectively, whereas SEQ ID NOs 60 and 70 corresponded to fragments "122-143" of them, and all contained the leptin fragment central sequence.

Besides the explicitly disclosed fragment sequences in example 10, the skilled person would also seriously contemplate further sequences implicitly disclosed. That the end-points of the explicitly disclosed fragments could also serve to define other fragments was directly apparent to the skilled person in view of the fact that both the initial fragments having the end-points in question were preferred embodiments of the invention and contained the leptin fragment central

sequence needed for the technical effect. The sequence consisting of amino acid residues "112 to 143" of human or mouse leptin was therefore also directly and unambiguously disclosed and fully in line with the teaching of the invention.

The conclusions in decisions T 2/81 and T 1063/96, which concerned overlapping concentration or temperature ranges, applied to the present case even though a peptide was not defined by a numerical range. The fragment "112 to 143" resulted from the combination of the lower end-point of the fragment "112-133" and the upper end-point of the fragment "122-143" and contained the leptin fragment central sequence.

Auxiliary request 1 - claim 1

The basis for the leptin polypeptide fragment consisting of amino acids 117 to 167 of human or mouse leptin was the lower end-point of the fragment "117 to 138" of human (SEQ ID NO: 57) or mouse leptin (SEQ ID NO: 67) and the upper end-point of the respective full-length leptin polypeptide, which both in humans and mice 167 amino acids long (see SEQ ID NO: 32 or SEQ ID NO: 34).

IX. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division with the order to grant a patent based on the main request filed with the letter of 2 October 2017, or, alternatively, based on auxiliary request 1 filed during the oral proceedings, and a description to be adapted thereto.

Reasons for the Decision

1. The appeal is admissible.

Added subject-matter

Main request - claim 1

2. The feature "*a sequence consisting of the amino acid residues 112 to 143 of a polypeptide sequence selected from the group consisting of SEQ ID NO: 32 or SEQ ID NO: 34*" defines a fragment of the human or mouse leptin polypeptide that modulates the activity of the lipolysis-stimulated receptor (LSR). In the decision under appeal the examining division considered this feature to contravene the requirements of Article 123(2) EPC.

3. According to Article 123(2) EPC a European patent application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. It has been established that the "gold standard" (G 2/10, OJ 2012, 376) for assessing compliance with Article 123(2) EPC is that any amendment to the parts of a European patent application relating to the disclosure (the description, claims and drawings) can only be made within the limits of what a skilled person would **derive directly and unambiguously**, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents as filed (see also decisions G 3/89, OJ EPO 1993, 117, and G 11/91, OJ EPO 1993, 125). It has further been established that subject-matter which is implicitly disclosed by the application as filed complies with the requirements of Article 123(2) EPC and that after the

amendment the skilled person may not be presented with new technical information (see decision G 2/10, *supra*).

4. In the present case, the application as filed discloses on page page 3, lines 11 to 18 that "[t]*he invention features the discovery of a 22 amino acid region of human leptin that modulates LSR activity in vitro and in vivo in the same way as the intact human leptin, (...). The new leptin fragment can also be used in disease treatment since it is active in mice at a physiologically-relevant level. In addition, the homologous region from mouse leptin was found to inhibit LSR activity in the human system, and is thus an LSR antagonist of the invention as well as being a powerful tool for identifying further modulators (both inhibitory and stimulatory) of LSR activity*." In the subsequent paragraph on page 3, lines 19 to 24, the application as filed then discloses in a more general manner that "[i]*n a preferred aspect, the invention features a leptin polypeptide fragment that modulates the activity of LSR, comprising at least 4, but not more than 50 contiguous amino acids of any one of the leptin polypeptide sequences set forth in Figure 13, wherein said at least 4 and not more than 50 contiguous amino acids comprise the leptin fragment central sequence. In preferred embodiments, the leptin polypeptide fragment comprises at least 10 but not more than 50, at least 20 but not more than 40, or at least 20 but not more than 30 contiguous amino acids*."

5. Having regard to the passages referred to above, the board concurs with the appellant that the application as filed relates, in general, to LSR-modulating leptin polypeptide fragments comprising 4 to 50 contiguous amino acids of e.g. the human or mouse leptin polypeptide sequences shown in Figure 13 and containing

the "*leptin fragment central sequence*". In particular, and also by reference to examples 7 and 8 of the application as filed, it was demonstrated that a 22-amino-acid region of leptin containing the leptin fragment central sequence is sufficient to modulate the activity of the LSR *in vitro* and *in vivo* in the same way as the intact human leptin.

6. On page 22, lines 11 to 13, the application as filed states that "[p]*referred embodiments of the invention feature a leptin polypeptide that consists of a sequence described in Example 10*". Example 10, on pages 81 to 83, of the application as filed has the title "*Molecular modelling of an active leptin fragment of the invention*" and discloses a molecular dynamic assay on both the human and mouse 22-amino-acid peptide as well as an *in-silico* combinatorial mutational assay of positions 126 to 129 positions of them. A number of peptides are disclosed in this context as the result of the assays. At the end of the example it is added that "[o]*ther peptides of the invention that can be tested in the assays described herein or other comparable assays for LSR agonistic or antagonistic activity include the following:*" followed by a table with ten particular partially overlapping human leptin peptide fragments (identified by their position in human leptin, the sequence and the corresponding SEQ ID NO) and another table with ten particular partially overlapping mouse leptin peptide fragments (identified by their position in mouse leptin, which is the same as in human leptin, the sequence and the corresponding SEQ ID NO). The length of the peptides varies between 10 and 22 amino acids.

7. The appellant argued not that the passages referred to explicitly disclose a sequence consisting of the amino

acid residues 112 to 143 of the human or mouse leptin polypeptide, but rather that besides the explicitly disclosed fragment sequences, the skilled person would also seriously contemplate further sequences implicitly disclosed in example 10. In particular, SEQ ID NOs 56 and 66 corresponded to the fragments "**112**-133" of human and mouse leptin respectively, and SEQ ID NOs 60 and 70 corresponded to fragments "122-**143**" of them, and all contained the leptin fragment central sequence. It was directly apparent to the skilled person that the end-points of the explicitly disclosed fragments, *i.e.* here "112" and "143", could also serve to define other fragments in view of the fact that both the initial fragments having the end-points in question were preferred embodiments of the invention and contained the leptin fragment central sequence needed for the technical effect. The sequence consisting of amino acid residues "112 to 143" of human or mouse leptin was therefore also directly and unambiguously disclosed and fully in line with the teaching of the invention.

8. The board cannot identify any disclosure in the passages in the application as filed referred to above from which the skilled person would derive directly and unambiguously that the end-points of the explicitly disclosed peptides are also suitable as end-points for other (implicitly disclosed) peptides. Human and mouse leptin fragments having sequences between newly combined end-points, *i.e.* such as between "112" and "143", are therefore not directly and unambiguously derivable from these passages.

9. The appellant furthermore argued that the conclusions of decisions T 2/81 (OJ EPO 1982, 394) and T 1063/96 of 27 September 2000 applied to the present case even though a peptide was not defined by a numerical range.

Accordingly, the fragment "112 to 143" resulted from the combination of the lower end-point of the fragment "**112**-133" and the upper end-point of the fragment "122-**143**" and contained the leptin fragment central sequence.

10. Both decision T 2/81 and T 1063/96, *supra*, concern the disclosure of overlapping concentration or temperature ranges and deal with the question whether or not newly defined ranges resulting from a combination of the end-points of the disclosed ranges constitute added subject-matter. In decision T 2/81, *supra*, the board held that the disclosure of a quantitative range of values (e.g. for concentration or temperature) together with an included preferred narrower range also directly disclosed the two possible part-ranges lying within the overall range on either side of the narrower range. Hence a simple combination of the preferred narrower range and one of these part ranges was also unequivocally derivable and is supported by the disclosure (Headnote 2). This principle was also applied to partly overlapping quantitative ranges in decision T 1063/96, *supra* (see point 3.1.1. of the Reasons).

11. The board notes that both concentration and temperature ranges constitute **quantitative definitions** of the parameter(s) in question. Newly defined ranges resulting from a combination of the end-points of the disclosed ranges do not lead to particular discrete concentrations or temperatures falling outside the explicitly disclosed ranges.

12. In the board's judgement a peptide fragment constitutes a discrete physical entity, made up of individual amino acids and having defined physical end-points, which is

not comparable to a range of a quantitative parameter within which the invention can be performed. Accordingly, the end-points of a peptide are also not comparable to the end-points of a quantitative parameter range. Furthermore, disclosure of two partly overlapping discrete peptide fragments does not also directly disclose the sequence of peptide fragments lying outside the overlap. The combination of particular end-points of two different discrete overlapping peptide fragments of a particular polypeptide to form a larger peptide fragment thus represents a different situation from the ones considered in decisions T 2/81 and T 1063/96, *supra*. Indeed, here the resulting peptide fragment constitutes a new discrete physical entity, *i.e.* a new **qualitative definition** of a product, which as such is not immediately apparent to the skilled person from the disclosure of two overlapping peptide fragments.

13. In view of these considerations the board has decided that claim 1 contains added subject-matter and so does not comply with the requirements of Article 123(2) EPC.

Auxiliary request 1 - claim 1

14. The arguments submitted by the appellant in support of the compliance with the requirements of Article 123(2) EPC of a claim for a leptin polypeptide fragment "*consisting of a sequence consisting of the amino acid residues **117** to **167** of a polypeptide sequence selected from the group consisting of SEQ ID NO: 32 or SEQ ID NO: 34*" (emphasis added by the board) were in essence similar to those in favour of the compliance of the subject-matter of claim 1 of the main request, whereby now reference was made to the lower end-point of the fragment "**117** to 138" of human

(SEQ ID NO: 57) or mouse leptin (SEQ ID NO: 67) and the upper end-point of the respective full-length leptin polypeptide, which both in humans and mice is 167 amino acids long (*i.e.* SEQ ID NO: 32 or SEQ ID NO: 34).

15. The board considers here too, however, that defining a new fragment by combining a particular end-point of a disclosed discrete peptide of a polypeptide with the first or last amino acid position of the disclosed full-length polypeptide results in a fragment which as such was not directly and unambiguously disclosed for the same reasons as in point 12. Accordingly, the board considers that the above findings in relation to claim 1 of the main request apply *mutatis mutandis* to claim 1 of auxiliary request 1.

16. In view of these considerations the board has decided that claim 1 contains added subject-matter and so does not comply with the requirements of Article 123(2) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona R. Morawetz

Decision electronically authenticated