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D E C I S I O N
of 24 May 2002

Case Number: W 0021/01 - 3.3.4

Application Number: PCT/EP 00/04561

Publication Number: WO-A-00/71682

IPC: C12N 9/52

Language of the proceedings: EN

Title of invention:
Crystal structure data of cysteinprotease Gingipain R

Applicant:
Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V. et al.

Headword:
Gingipain/MAX PLANCK

Relevant legal provisions:
PCT Art. 17.3(a)
PCT R. 13.1, 13.2, 13.3, 40.1, 40.2(c), 40.2(e)

Keyword:
"Lack of unity or posteriori (yes)"

Decisions cited:
W 00 13/87, G 0001/89

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0021/01 - 3.3.4
International Application No. PCT/EP 00/04561

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 24 May 2002

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Subject of the Decision: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 12 December 2000.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
B. Günzel

Summary of Facts and Submissions

I. International patent application PCT/EP 00/04561 (published as WO-A-00/71682) was filed on 19 May 2000 with twenty-four claims.

Claims 1, 2, 5, 6 and 7 read as follows:

"1. Crystal structure of gingipain R as shown in Fig.1."

"2. Crystal structure of gingipain R in complex with the H-D-Phe-Phe-Arg-chloromethylketone as shown in Fig. 2 and Fig.4."

"5. Gingipain R-inhibitor characterized in that it is able to specifically bind to and/or interact with D163 in the P1-pocket of gingipain R and in that it has a nitrile, diazomethlyketone, acyloxymethylketone, methlysulfonium salt, epoxysuccinyl derivative, vinylsulfone, O-acylhydroxamate, aziridine or activated disulfide group that forms a covalent, hydrolytically stabile bond to the enzyme."

"6. Gingipain R-inhibitor, characterized in that it binds non-covalently to the enzyme or forms a covalent, hydrolytically labile bond to the enzyme, and in that it specifically binds to and/or interacts with D163 in the P1-pocket of gingipain R."

"7. Gingipain R-inhibitor according to claim 6, that has an aldehyde, methlyketone or trifluoromethlyketone, α-ketoacid, -ester or amide or diketone group that forms a covalent, hydrolytically labile bond to the enzyme."

Claims 3 and 4 related to the use of the crystal structure according to claim 1 or 2 for designing and/or identifying inhibitors of gingipain R.

Dependent claims 8 to 16 concerned particular embodiments of the gingipain R-inhibitor according to claims 5 to 7. Claims 17 related to a gingipain R-inhibitor with formula (III) for which the substituents R1, R2 and R3 were not defined. Dependent claims 18 to 20 related to particular embodiments of claim 17. Claims 21 and 22 were directed to a pharmaceutical composition containing as an active agent a gingipain inhibitor according to claims 5 to 20. Claim 23 was directed to the use of such pharmaceutical composition for treating or preventing specific diseases, while claim 24 was directed to the use of a gingipain R-inhibitor for the production of a pharmaceutical composition.

II. On 12 December 2000 the European Patent Office (EPO), acting as an International Search Authority (ISA), invited the applicants to pay within a time limit of 30 days two additional search fees pursuant to Article 17(3)(a), Rule 40.1 and 40.3 PCT and issued a partial search report on claims 1 to 4. The invitation stated the 3 groups of inventions to which the application was found to relate, namely:

(1) **Claims 1 to 4**: Crystal structure of gingipain R and its use;

(2) **Claim 5 and claims 8 to 24 (partially)**: Covalently bound gingipain R inhibitors and their use;

(3) **Claims 6 to 7 and claims 8 to 24 (partially)**: Non-covalently or unstably covalently bound gingipain R inhibitors and their use.

The reasons for the non-unity finding were indicated as being essentially that, since gingipain R crystals and covalently bound gingipain R-inhibitors were known from Protein Science (1998), Vol. 7, pages 1259 to 1261, there was neither a technical relationship between the use of the crystals and the different groups of inhibitors of the enzyme nor a further special technical feature which provided a single inventive concept for the plurality of inventions.

III. On 10 January 2001 the applicants paid two additional fees under protest pursuant to Rule 40.2(c) PCT and provided a reasoned statement to the effect that the international application complied with the requirement of unity of invention. They submitted that the three-dimensional crystal structure of gingipain R and the knowledge of its active site were not known from the cited reference. Only this information which was made available for the first time by the application allowed the development of suitable inhibitors. In fact, only the indication of the anchor site to which an inhibitor molecule at least should bind, whether covalently or non-covalently, stably or unstably permitted the design of the inhibitors.

IV. On 7 May 2001, the ISA transmitted the International Search Report. This was not established in respect of claims 19 and 20 which were considered to be unsearchable because they were unclear and unsupported by the description so that no meaningful search was possible, and in respect of claim 23, which related to a method of treatment of the human/animal body.

V. On the same date, the ISA communicated to the applicants the result of its review under Rule 40.2(e) PCT and ordered the refund of one additional search fee as "the extra necessary search effort for invention 2 and 3 did not justify the levying of two additional

search fees". However, the presence of two separate groups of inventions and, consequently, the need for the payment of one additional fee was confirmed essentially for the following reasons:

- The question whether the claimed crystal structure was known from the cited reference was irrelevant for the question of unity;

- Relevant was the fact that crystals of gingipain R and inhibitors thereof were known and, consequently, also methods for preparing or screening the inhibitors without the need of the precise knowledge of the crystal structure;

- Thus, there was no inventive concept linking **claims 1 to 4 (group 1)**, which concerned the crystal structure of gingipain R and its use, to **claims 5 to 24 (group 2)**, which related to covalently bound or non-covalently bound or unstably covalently bound gingipain R inhibitors and to their use.

VI. The protest fee was paid by the applicants on 6 June 2001 in conformity with Rule 40.2(e) PCT.

Reasons for the Decision

1. The protest is admissible.

2. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. As stated in Rule 13.2 PCT, this requirement is fulfilled only when there is a technical relationship among those inventions involving one or

more of the same or corresponding "special technical features", these being those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

If the ISA considers that the claims lack this unity, it is empowered, under Article 17(3)(a) PCT, to invite the Applicant to pay additional fees.

3. Lack of unity may be directly evident *a priori*, ie before the examination of the merits of the claims in comparison with the state of the art revealed by the search (cf, for example, decision W 13/87 of 9 August 1988). Alternatively, an objection can also be raised *a posteriori*, ie after having taken the prior art revealed by the search into closer consideration. This practice is laid down in the PCT Preliminary Examination Guidelines, Chapter III, 7 (PCT/GL/3 dated 1 March 1993) and in Section 206 and Annex B to the Administrative Instructions (cf PCT GAZETTE, Special Issue, 25 June 1998) which are the basis for a uniform practice of all International Searching and Examining Authorities. Such consideration of the prior art represents only a provisional opinion on novelty and inventive step which is in no way binding upon the authorities subsequently responsible for the further examination of the application (cf decision G 1/89 of the Enlarged Board of Appeal, OJ EPO 1991, 155, see in particular point 8.1. of the Reasons).

4. According to Rule 13.3 PCT, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

5. The question in the present case is whether or not a "special technical feature" can be seen to link the claims of groups 1 and 2 so as to form a single general inventive concept.

6. Claim 1 (group 1) is directed to a "crystal structure of gingipain R as shown in Fig. 1". As stated in the legend on page 30, Figure 1 is the ribbon plot of the gingipain molecule. Claim 2 (group 1) is directed to the crystal structure of gingipain R in complex with the H-D-Phe-Phe-Arg-chloromethylketone (FFRCMK) as shown in Figure 2 and Figure 4. Figure 2 is a schematic drawing of the interaction of FFRCMK with gingipain, while Figure 4 is a representation of the interaction of FFRCMK with the active site. It has to be observed that the definition of the products in question by reference to figures which convey information in terms of a plot or a scheme is not considered to be technically meaningful for a comparison with the prior art products.

7. At any rate, the preparation of crystals of gingipain R2, in particular in complex with the known inhibitor FFRCMK, and their preliminary X-ray diffraction analysis is known from the quoted Protein Science citation (supra). There is no evidence to the effect that the crystals made available by this prior art are in any respect different in their structure from those of the present application, both being obtained by a vapor diffusion method. The elucidation of the crystal structure and its characterisation by reference to a figure cannot per se confer novelty to known crystals, as this is only additional information obtained by further analysis which does not change the intrinsic nature and structure of the product. Thus, in the absence of evidence to the contrary, the board has to assume that claims 1 and 2 lack novelty.

8. Claims 5 to 7 (group 2) are product claims directed a large group of gingipain R-inhibitors which are broadly defined either in terms of their ability to bind and/or interact with residue D163 (ie aspartic acid in position 163) in the P1 pocket of the molecule (cf claim 6) or in terms of the presence of chemical groups (cf claims 5 and 7) which bind and/or interact with the said residue D163. The known compound FFRCMK (cf loc. cit.) is one of such inhibitors which - as shown by the application - satisfies the conditions of eg claims 6 and 7, ie it interacts with residue D163. Although it might not have been known in the art that the inhibitory activity of said compound involved inter alia such an interaction, the elucidation that it is so does not change the intrinsic structure of the known inhibitor. As a matter of fact, due to the broad "reach-through" formulation of the claims in question, it cannot be excluded that other known compounds might well interact in the same manner with the active site of gingipain. Thus, the novelty of the quoted claims is affected at least by the known product FFRCMK.

9. As product claims 1 and 2 of group 1 and product claims 6 and 7 of group 2 lack novelty there cannot be a "special technical feature" which links together the two groups of inventions to form a single inventive concept. The fact that the additional information allegedly provided by the present application about the structure of the crystals and the site of bonding and/or interaction of the inhibitors (including known inhibitors such as FFRCMK) allows now the design and/or identification of inhibitors of gingipain, while possibly constituting a basis for the formulation of use or method claims, cannot constitute a link between two groups of generally formulated product claims which lack novelty.

10. For the foregoing reasons, the international application does not comply with the requirement of Rule 13.1 PCT and the invitation to pay an additional fee was justified.

Order

For these reasons it is decided that:

The protest under Rule 40.2(c) PCT is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey