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Datasheet for the decision of 19 November 2020

Case Number: T 1798/18 - 3.3.07

Application Number: 10703808.5

Publication Number: 2393518

IPC: A61K47/48, G01N33/68

Language of the proceedings: EN

Title of invention:
STRUCTURED POLYCYCLIC PEPTIDE

Applicant:
BicycleRD Limited

Headword:
Structured polycyclic peptide / BICYCLERD

Relevant legal provisions:
EPC Art. 56, 87(1), 111, 123(2)
RPBA Art. 13(1), 13(3)

Keyword:
Late-filed auxiliary requests - admitted (yes)
Amendments - added subject-matter (no)
Priority - basis in priority document (no)
Inventive step - after amendment

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Case Number: T 1798/18 - 3.3.07

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

Appellant: (Applicant)	BicycleRD Limited B900 Babraham Research Campus Cambridge CB22 3AT (GB)
Representative:	Maschio, Antonio Maschio & Soames IP Limited 30 Carlton Crescent Southampton SO15 2EW (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 8 March 2018 refusing European patent application No. 10703808.5 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	Y. Podbielski

Summary of Facts and Submissions

I. The appeal was filed by the applicant (hereinafter: "the appellant") against the decision of the examining division to refuse the European patent application 10703808.5.

II. The appealed decision was based on a main request and auxiliary requests 1 and 2, all filed on 3 January 2018.

Claim 1 of the main request related to a repertoire of scaffolded peptide ligands, wherein cyclised polypeptides variants form n loops by n attachments to a molecular scaffold with n-fold symmetry wherein n is 2 or 3. Dependent claim 9 defined the further feature that the repertoire is displayed using a genetic display system.

The decision under appeal cited *inter alia* the following documents:

D3: WO 2009/098450
D4: TETRAHEDRON LETTERS, vol. 22, no. 46, 23 March 1981 (1981-03-23), pages 4571-4574,
D5: THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 284, no. 49, 4 December / 6 October 2009(2009-10-06), pages 34126-34134.

According to the decision under appeal the subject-matter of claim 1 of the main request differed from the teaching of the closest prior art, document D4, in that it related to a repertoire of peptide ligands rather than an individual peptide ligand. The problem to be solved was seen in the provision of a repertoire of

peptide ligands with relative ease. Document D4 itself mentioned that the syntheses and study of analogs with expected favourable solubility was in process. It was further well known to the skilled person that a repertoire of peptide ligands can be used for screening candidate compounds as illustrated by the documents cited in the application. The mere provision of more than one peptide ligand or a repertoire of peptide ligands was therefore obvious to the person skilled in the art. Accordingly, claim 1 did not comply with the requirements of Article 56 EPC

Claim 1 of auxiliary request 1 did not meet the requirement of inventive step for essentially the same reasons as set out for claim 1 of the main request.

The description remained unamended and referred to the invention in terms not covered by the amended claims of the requests on file. The main request and auxiliary requests 1 and 2 did therefore not meet the requirements of Article 84 EPC.

III. 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 the claims of the main request or one of auxiliary requests 1 and 2 as considered by the Examining Division in the appealed decision.

IV. The appellant was summoned to oral proceedings by letter dated 16 July 2019. In a communication pursuant to Article 15(1) RPBA the Board questioned whether the claimed subject-matter was specifically disclosed in the priority documents and indicated that without priority entitlement the cited documents D3 and D5 represented relevant alternative starting points in the

prior art for the assessment of the requirement of inventive step. The Board further identified the following documents as relevant:

D6: WO2004/077062
D7: WO2006/078161

V. During the oral proceedings held on 19 November 2020, in which the Board announced that the subject-matter of the mentioned dependent claim 9 involved an inventive step, the appellant filed a new main request with an amended set of claims in which the repertoire of peptide ligands is further defined as displayed using a genetic display system.

VI. The appellant's arguments can be summarized as follows:

Document D3 described the cyclisation of polypeptides attached via 3 bonds to a molecular scaffold forming 3 loops by joining the N- and C-termini (*in the following also referred as "ultimately cyclized polypeptides"*). The document did not mention a repertoire of such ultimately cyclized polypeptides which is displayed using a genetic display system. The present application disclosed methods for the ultimate cyclisation that were compatible with the presence of a genetic display system. The prior art provided no suggestion towards scaffolded polypeptides which retain a genetic display following the ultimate cyclisation.

VII. The appellant requested that that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed during the oral proceedings.

Reasons for the Decision

Main request

1. Admittance

Claim 1 of the main request submitted during the oral proceedings relates to:

"A repertoire of peptide ligands which is displayed using a genetic display system, wherein each peptide ligand comprises a polypeptide variant linked to a molecular scaffold at n attachment points, wherein said polypeptide is cyclised and forms n separate loops subtended between said n attachment points on the molecular scaffold, wherein n separate loops = n attachment points and n is 2 or 3, and said molecular scaffold possesses n scaffold reactive groups and n-fold molecular symmetry."

Dependent claims 2-5 define further aspects of such a repertoire.

Claim 1 of this request incorporates the features of claim 1 and dependent claim 9 of the preceding main request. The Board has admitted this request as a legitimate response to the Board's announcement during the oral proceedings that the defined subject-matter was considered to involve an inventive step (Article 13(1)and (3) RPBA 2007).

2. Article 123(2) EPC

In view of *inter alia* the disclosure on pages 3, 8 and 10 and the definitions in claims 1, 3, 5-7 and 9-12 of

the application as originally filed the Board is satisfied that the main request complies with the requirements of Article 123(2) EPC.

3. Priority

The definition of the scaffolded peptide ligands in claim 1 implies that the polypeptides form themselves a cycle which is further divided in 2 or 3 loops by the attachments to the scaffold.

The priority documents PCT/GB2009/000301 (P1) of 4 February 2009 and GB0913775.3 (P2) of 6 August 2009 mention such ultimately cyclised peptides, but only in the context of tricyclic structures formed by N- to C-cyclisation of polypeptides attached to a molecular scaffold (see P1, page 46-47 and P2 page 45). Moreover the priority documents specifically state that the formation of these tricyclic structures is suitably carried out on a polypeptide-connector compound conjugate and is suitably not carried out on phage (see P1, page 46, lines 37-38 and P2, page 45, lines 10-13). The priority documents do thereby not specifically describe a collection the tricyclic structures, let alone a repertoire of such structures which is displayed using a genetic display system as defined in the claims of the main request. The priority entitlement is therefore denied (Article 87(1) EPC).

Accordingly, the relevant date for determining the prior art with respect to the application is the filing date, 4 February 2010. Document D3 (published 13 August 2009), which corresponds to the priority application P1, therefore represents prior art under Article 54(2) EPC.

4. Inventive step

4.1 Document D3 is considered to represent the closest prior art. This document describes the generation of a genetically encoded combinatorial chemical library comprising polypeptides tethered to a molecular core via at least three bonds, which allows screening and isolation of relevant members (see page 45, line 34 to page 46, line 2). The document further describes tricyclic structures of peptides joined to a connector compound, which may be created by N- to C-cyclisation of bicyclic structures of the peptides linked to the connector compound (see page 46, line 32 to page 47, line 20). Such tricyclic structures correspond to the scaffolded polypeptide ligands as defined in the claims of the main request. However, document D3 does not specifically describe a repertoire of these ultimately cyclized tricyclic structures.

4.2 The subject-matter as defined in the claims of the main request differs from the teaching of document D3 in that the ultimately cyclised scaffolded polypeptides are assembled in the form of a repertoire displayed by a genetic display system.

Repertoires of compounds are useful in large scale screening and selection of compounds that exhibit a desired activity (see page 8, lines 21-31 of the application). The genetic display serves the purpose of identification and propagation (compare page 14, lines 23-28 of the application). The present application describes a mild and specific enzymatic cyclisation method for the relevant cyclisation of polypeptides by ligation of lysine and glutamine side chains (see pages 30-34). In this context the application specifically suggests that such cyclisation can be carried out in

the presence of mixtures of proteins such as in the cytoplasm or a mammalian or bacterial cell (see page 31, chapter "Catalytic activity of MTGase...", lines 23-27). In view of this information the Board is satisfied that the application renders the assembly of a repertoire of the cyclised peptides with a genetic display feasible.

Accordingly, the problem to be solved may be seen in the provision of a system for convenient large scale investigation of the ultimately cyclised scaffolded polypeptides.

4.3 Document D3 itself refers to the advantages of library technology using a genetic display system, such as a phage display library, and teaches the application of such technology to structures of scaffolded polypeptides (see page 38, lines 14-29). However, where document D3 discusses the ultimate cyclisation of scaffolded polypeptides to form tricyclic structures by joining N- to C-termini, it specifically teaches that such cyclisation is carried out on a polypeptide-connector compound conjugate. In this context the document explicitly mentions that the ultimate cyclisation is not suitably carried out on phage, which represents the exemplary genetic display system in document D3 (see page 46, lines 37-38). Document D3 therefore provides the skilled person, who is faced with the above identified problem, with no relevant suggestion towards the claimed subject-matter.

Documents D6 and D7 are discussed in document D3 (see page 46). These documents indicate that library technology may be applied to scaffolded polypeptides. However these documents do not refer to a genetic display system and provide the skilled person with no

relevant suggestion towards the claimed repertoire of ultimately cyclised scaffolded polypeptide displayed with a genetic display system.

The Board therefore concludes that having regard to the available prior art the subject-matter defined in the claims of the main request was not obvious to the skilled person and thus involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division with the order to grant a patent on the basis of the main request filed during the oral proceedings on 19 November 2020 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated