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Datasheet for the decision of 8 August 2024

Case Number: T 1289/22 - 3.3.08

Application Number: 15709505.0

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Title of invention:
TCR LIBRARIES

Patent Proprietor:
Immunocore Limited
Adaptimmune Limited

Opponent:
Michalski Hüttermann & Partner
Patentanwälte mbB

Headword:
TCR libraries/IMMUNOCORE LIMITED & ADAPTIMMUNE LIMITED

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)
Amendment after summons - admission (no)

Decisions cited:
T 0578/06, T 2044/09, T 1791/08, T 0688/14

Catchword:

Europäisches Patentamt
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Beschwerdekammern

Boards of Appeal

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Case Number: T 1289/22 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 8 August 2024

Appellant: (Opponent)	Michalski Hüttermann & Partner Patentanwälte mbB Kaistraße 16A 40221 Düsseldorf (DE)
Representative:	Storz, Ulrich
Respondent: (Patent Proprietor 1)	Immunocore Limited 101 Park Drive Milton Park Abingdon, Oxfordshire OX14 4RY (GB)
Respondent: (Patent Proprietor 2)	Adaptimmune Limited 9400 Garsington Road Oxford Business Park Oxford OX2 2HN (GB)
Representative:	Lau, Sarah Nick, Amy Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 March 2022 rejecting the opposition filed against European patent No. 3116901 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Pilat
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 3 116 901 is based on European patent application No. 15 709 505.0, originally filed as international patent application published as WO 2013/136072. The patent was opposed under Article 100(a) in conjunction with Articles 54 and 56 EPC, and under Article 100(b) EPC.

II. The opponent (appellant) lodged an appeal against the opposition division's decision rejecting the opposition.

III. With its reply to the statement of grounds of appeal (RSoG), the patent proprietor (respondent) requested that the appeal be dismissed (main request) or alternatively be maintained based on auxiliary requests 1 to 7, 2a to 7a, 2b to 7b and 2c to 7c.

IV. The **main request** consists of the patent as granted, while **auxiliary request 1** corresponds to the main request, except that paragraph [0066] of the description was deleted.

V. Claims 1 and 11 of the **main request** and of **auxiliary request 1** read as follows:

"1. A library of particles, the library displaying a plurality of different T cell receptors (TCRs), wherein the plurality of TCRs consists essentially of TCRs comprising an alpha chain comprising an alpha chain variable domain from a natural repertoire and a beta chain comprising a beta chain variable domain from a natural repertoire, wherein the alpha chain variable domain comprises a TRAV12-2 or a TRAV21 gene product

and the beta chain variable domain comprises a TRBV6 gene product.

11. A method of making a library of particles, the library displaying a plurality of different TCRs, the method comprising:
i) obtaining a plurality of nucleic acids from a natural repertoire that encode different TRAV12-2 or TRAV21 alpha chain variable domains;
ii) obtaining a plurality of nucleic acids from a natural repertoire that encode different TRBV6 beta chain variable domains;
iii) cloning the TRAV12-2 or TRAV21 alpha chain variable domain encoding nucleic acids into expression vectors;
iv) cloning the TRBV6 beta chain variable domain encoding nucleic acids into the same or different vectors; and
v) expressing the vectors in particles, thereby generating a library consisting essentially of TCRs comprising an alpha chain variable domain and a beta chain variable domain encoded by the nucleic acids."

VI. In **auxiliary request 2b** claims 1 and 11 as granted were amended to refer to a plurality of different TCRs **"having variation in CDR3 length"**.

VII. In **auxiliary requests 3b**, **4b** and **5b** claim 1 as granted was amended as shown: "...(a) the plurality of TCRs consists essentially of TCRs comprising an alpha chain comprising an alpha chain variable domain ~~from a natural repertoire and a beta chain comprising a beta chain variable domain from a natural repertoire, wherein the alpha chain variable domain~~ comprising ~~es~~ a TRAV12-2 or a TRAV21 gene product and ~~the~~ a beta chain comprising a beta chain variable domain comprising ~~es~~ a

TRBV6 gene product; and **(b) the alpha and beta chain variable domains of said TCRs are expressed from DNA sequences that have been obtained from human donors"**. Claim 1 of **auxiliary request 4b** was further amended to specify that the plurality of TCRs **"consists of 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%** ~~essentially~~ of TCRs comprising an alpha chain comprising an alpha chain variable domain comprising a TRAV12-2 or a TRAV21 gene product and a beta chain comprising a beta chain variable domain comprising a TRBV6 gene product; ...".

VIII. In **auxiliary request 6b** claims 1 to 10 as granted were deleted, so that claim 11 as granted became claim 1.

IX. Claim 1 of **auxiliary request 7b** corresponds to claim 1 of **auxiliary request 6b** except that the reference to "a natural repertoire" was replaced by **"from human donors"**.

X. The following documents are referred to in this decision:

D1 WO 2005/116074
D16 "The T cell receptor" FactsBook, Marie-Paule Lefranc, Gérard Lefranc, Academic Press, 2001, ISBN 0-12-441352-8

XI. The parties' submissions, insofar as they are relevant to the decision, are discussed in the Reasons for the Decision, below.

XII. The appellant requests that the decision under appeal be set aside and the patent be revoked in its entirety. It moreover requests that none of the new documents D23 to D27 and of the auxiliary requests be admitted.

XIII. The respondent requests that the appeal be dismissed and that the patent be maintained as granted (main request). Alternatively, it requests that the patent be maintained based on the claims of auxiliary requests 1 to 7, 2a to 7a, 2b to 7b and 2c to 7c in the following order: 1, 2, 2a, 2b, 2c, 3, 3a, 3b, 3c, 4, 4a, 4b, 4c, 5, 5a, 5b, 5c, 6, 6a, 6b, 6c, 7, 7a, 7b, and 7c. It moreover requests that documents D23 to 27 be admitted.

Reasons for the Decision

Admittance of documents D23 to D27 (Articles 12(4) and 13(2) RPBA)

1. The respondent submitted new documents D23 to D26 with its response to the statement of grounds of appeal (RSoG), while document D27 was announced in the RSoG but was only submitted with a later letter. The justification for the submission of documents D23 to D27 in appeal was only provided with said later letter, dated 18 June 2024 and filed in reaction to the appellant's letter dated 2 February 2024, after summons for oral proceedings before the board were issued on 13 November 2023.

2. According to Article 12(4) RPBA, any part of a party's appeal case which does not meet the requirements in Article 12(2) RPBA is to be regarded as an amendment, which may be admitted only at the discretion of the board, and the party shall clearly identify each amendment and provide reasons for submitting it in the appeal proceedings. Since the respondent has not complied with the latter requirements of Article 12(4) RPBA, the board sees no reason to admit these documents under this provision.

3. In view of the timing on which the amendment of case, i.e. newly submitted documents, was justified, admittance of documents D23 to D27 needs to be considered under Article 13(2) RPBA of the version of the Rules of Procedure which was valid at the date when summons for oral proceedings were sent, namely the version published in OJ EPO 2021, A35 (see Article 25(3) RPBA of the revised version published in OJ EPO 2024, A15). Article 13(2) RPBA in the relevant version states that such amendments shall in principle not be taken into account unless there are exceptional circumstances which have been justified by cogent reasons by the party concerned. The respondent's argument that the documents had been filed in reaction to the decision of the opposition division could be a suitable justification under Article 12(4) RPBA but does not establish any exceptional circumstances justified by cogent reasons, as required by Article 13(2) RPBA. Hence the board decided not to admit documents D23 to D27 into the appeal proceedings.

Main request
Inventive step - claims 1 and 11

Closest prior art and distinguishing features

4. The patent relates to a library of particles, the library displaying a plurality of different T cell receptors (TCRs), wherein the plurality of TCRs consists essentially of TCRs comprising an alpha chain variable domain from a natural repertoire and a beta chain variable domain from a natural repertoire, wherein the alpha chain variable domain comprises a TRAV12-2 or a TRAV21 gene product and the beta chain variable domain comprises a TRBV6 gene product

(paragraph [0001]). This library enables the more reliable identification of functional TCRs and may be screened using a variety of peptide antigens in order to identify useful TCRs (paragraph [0019]).

5. The board considers that the disclosure of document D1 is a suitable starting point for the discussion of inventive step of claim 1. This was not disputed.

6. It is also undisputed that the claimed subject-matter differs from the disclosure of document D1 in that the alpha chain variable domain of the claimed library comprises a TRAV12-2 or a TRAV21 gene product and the beta chain variable domain comprises a TRBV6 gene product. While the respondent identified as further distinguishing feature that the number of chains was reduced to include only specific gene loci, the board agrees with the appellant (and the appealed decision, point 19.5 of the Reasons) that in fact this difference is already part of the above identified distinguishing feature, i.e. the subject-matter is limited to TRAV12-2 or TRAV21 alpha chains variable domains and TRBV6 beta chain variable domains.

Technical effect attributed to the distinguishing features

7. The data in the patent do not allow to attribute any technical effect linked to the distinguishing feature(s) over document D1. Nor has such an effect been demonstrated by any additional data on file. Hence, in agreement with the appellant and the decision under appeal (point 19.6 of the Reasons), the board considers that there is no technical effect associated with this distinguishing feature.

8. The respondent disagreed that there was no technical effect associated with the distinguishing features, arguing that the claimed libraries allowed the identification of functional, specific and potentially therapeutic TCRs, where previous library design strategies such as those generated by T cell cloning had failed. The board notes however that the technical effect must be defined in relation to the closest prior art document D1 and attributed to the distinguishing features identified in relation to document D1. Hence any technical effects obtained in comparison with other library design strategies, such as T cell cloning, are not to be considered when defining a technical effect over the closest prior art document D1.

9. The respondent moreover argued that the library generated in document D1 did not work, and that this was because the diversity of the TCRs libraries generated by an "all chain" approach included TCRs with inappropriate or suboptimal alpha/beta chain pairings, a large number of cross-reactive and non-functional TCRs, preventing the identification of functional TCRs. The board however notes that there is no factual evidence for these allegations; the statement in paragraph [0018] of the patent according to which TCR clones isolated from document D1's library were not peptide-specific is in contrast to the whole disclosure of document D1 and cannot be taken as evidence for failure of document D1's library as a whole. On the contrary, the board notes that document D1 discloses the isolation of TCRs binding to a target peptide-MHC complex from the diverse phage library displaying native TCR variable domains (Example 2 starting on page 36) and that phage clones that bind to the SLLMWITQC-HLA-A*0201 complex were indeed found during the ELISA screening due to their strong ELISA signals relative to

control wells. Document D1 demonstrates that TCRs with the desired specificity have been isolated from said library. Thus the argument that the library is non-functional must fail. In addition, there is no evidence either for the respondent's allegation that reducing the number of chains to include only specific gene loci, and particularly TRAV12-2, TRAV21 and TRBV6, was associated with a technical effect at all, let alone the provision of a highly effective TCR discovery strategy, as argued by the respondent.

10. Finally, as regards respondent's argument that, as concluded in decision T 578/06, experimental data and results are not required by the EPC to demonstrate that the claimed subject-matter solves the objective technical problem, this does not mean that a technical effect attributed to the distinguishing features in relation to the closest prior art does not have to be made plausible, by means of comparative examples or in some other way. This decision is therefore not relevant in the context of the definition of the technical effect.

Objective technical problem

11. Since there is no technical effect associated with the distinguishing feature(s) identified above, the technical problem is to be formulated, in agreement with the appellant, as the provision of an alternative TCR library. In this context, the board disagrees with the formulation of the technical problem in the appealed decision, which already includes elements of the solution, namely that the library is to comprise "encoded specific alpha and beta chains" (appealed decision, point 19.7 of the Reasons). The board also disagrees with the respondent that the technical

problem to be solved may be formulated as the provision of a diverse library including a plurality of specific alpha and beta chain gene products obtained from a natural repertoire, which can be screened with a variety of different peptide antigens and used to identify functional, specific and potentially therapeutic TCRs: the formulation of the objective technical problem has to be based on the identified technical effect and, as discussed above, none of these functional properties can be seen as a technical effect over the disclosure of the closest prior art document D1.

Solution and obviousness

12. The board is convinced that the objective technical problem as formulated above is solved by the claimed library. However, the board considers that the claimed solution lacks an inventive step because it would be obvious to the skilled person, faced with the objective technical problem defined above, to provide alternative TCR alternatives, the specifically claimed TCR library being just one possible option. Since the objective technical problem is the provision of an alternative display library, any library generated using a subset of alpha chain variable domain gene product and beta chain variable domain gene product already used in a different combination in document D1, which uses 43 alpha chain variable domains and 37 beta chain variable domain out of 44 to 46 and 40 to 48 possible functional chain types, respectively (document D16, page 48, first line of the second paragraph and page 59, last line), is an equally suitable solution to the technical problem posed. The mere selection of particular specific loci, such as TRAV12-2 or TRAV21 alpha chain variable domains and a TRBV6 beta chain variable

domain, among all the alpha chain and beta chain variable domains disclosed in document D1 must be seen as arbitrary, for which no pointer or incentive is required, and cannot constitute the basis for acknowledging an inventive step.

13. As regards the respondent's assertion that the claimed solution is not one of "several obvious solutions", but, rather, the first successful attempt at using a library-based strategy for identifying novel TCRs, the board disagrees since, as discussed above (see point 9. above), the library generated in document D1 allowed the successful identification of TCRs and there is no evidence for a technical advantage of the claimed library over the libraries disclosed in document D1.

14. Although the skilled person is defined in the case law as being cautious and having a conservative attitude, it is also acknowledged that it is within the normal tasks of a skilled person to further develop the existing state of the art by routine adaptations and use of known alternatives (cf. T 688/14, point 25.1 of the Reasons). Where the objective technical problem is the provision of a mere alternative solution, if the modification and distinguishing feature over the prior art is not linked to a particular functionality, then no inventive step can be acknowledged based on this feature (decision T 2044/09).

15. For the sake of argument, even if TCRs identified using document D1's library, a library with broad and shallow diversity across the whole natural repertoire, will inevitably differ from those identified using a library in accordance with claim 1, with narrow and deep diversity across the natural repertoire of a small number of chains, still this particular choice does not

confer any technical effect beyond the library of document D1 (e.g. points 7. and 9. above). Nor does it constitute a non-obvious solution to the library disclosed in document D1, since the claimed alpha or beta variable chain domain had already been used to generate a display library of TCRs (e.g. document D1) and there was no technical prejudice against this choice. The conclusions of decision T 1791/08, reasons 12.5 and 13.1, that the claimed solution was non-obvious do not therefore apply. Thus, the skilled person faced with the technical problem identified above would not have been precluded from generating a library of particles according to claim 1, wherein the alpha chain variable domain comprises a TRAV12-2 or a TRAV21 gene product and the beta chain variable domain comprises a TRBV6 gene product.

16. Accordingly, the subject-matter of claim 1 of the main request does not fulfil the requirements of Article 56 EPC. The same applies to claim 11 which is directed to the method for obtaining a library as claimed in claim 1 and also only differs from document D1 in that nucleic acids encoding TRAV12-2 or a TRAV21 alpha chain variable domains and TRBV6 beta chain variable domains are used.

Admittance of auxiliary requests 1 and 2b to 7b

17. In view of the board's conclusion on inventive step (see below), there is no need for the board to give reasons for having decided to take auxiliary requests 1 and 2b to 7b into account and to consider them in substance.

Auxiliary request 1

18. Auxiliary request 1 is identical to the main request except that paragraph [0066] of the description has been deleted.

19. Since the claims of the main request and of auxiliary request 1 are identical and since the presence or absence of paragraph [0066] of the description has no effect on them, the lack of inventive step found for the main request also applies to auxiliary request 1.

Auxiliary request 2b

20. In auxiliary request 2b claims 1 and 11 have been amended to refer to a plurality of different TCRs "having variation in CDR3 length".

21. Since it is well within the common general knowledge of a skilled person that retaining or having variation in CDR3 length is an inherent property of natural repertoire libraries, as admitted by the respondent in section 7.2.10 of the RSoG, the technical feature introduced in claims 1 and 11 of auxiliary request 2 does not constitute a further distinguishing feature over document D1. Consequently, the lack of inventive step found for the main request also applies to auxiliary request 2b.

Auxiliary requests 3b to 5b

22. In auxiliary requests 3b, 4b and 5b claim 1 as granted has been amended by deleting the references to "a natural repertoire" and specifying instead that "the alpha and beta chain variable domains of said TCRs are expressed from DNA sequences that have been obtained from human donors". In auxiliary request 4b, claim 1 has been further amended by replacing "consisting

essentially of..." with "consists of 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% of...".

23. Since the diversity of the TCR alpha and beta chains in the library of document D1 also derives from human donors, this technical feature hence does not constitute a further distinguishing feature over the display library of TCRs of document D1. As to the further amendment in auxiliary request 4b, no arguments have been provided by the respondent as to why this amendment should render the claim inventive. Thus the lack of inventive step as regard the subject-matter of the main request also applies to the subject-matter of auxiliary requests 3b, 4b and 5b.

Auxiliary request 6b

24. Auxiliary request 6b corresponds to claims 11 to 14 as granted, whereas claims 1 to 10, 15 and 16 as granted have been deleted.

25. Since the subject-matter of the method claim 11 of the main request and claim 1 of auxiliary request 6b is identical, the lack of inventive step found in point 16. above as regard the method of the main request also applies to auxiliary request 6b.

Auxiliary request 7b

26. In auxiliary request 7b claim 1 of auxiliary request 6b has been further amended by replacing the reference to "a natural repertoire" with "from human donors".

27. For the same reasons as discussed above for auxiliary requests 3b, 4b, 5b and 6b, auxiliary request 7b also lacks an inventive step.

28. In summary, none of auxiliary requests 2b to 7b comply with Article 56 EPC.

Admittance of auxiliary request 2 to 7, 2a to 7a and 2c to 7c

29. All these auxiliary requests have been submitted for the first time with the RSoG. When submitting the auxiliary requests, the respondent has not provided any reasons as to why these auxiliary requests could only have been filed with the reply to the appeal and not already during opposition. Unless the reasons justifying their admittance are self-explanatory, such claim requests are only deemed to have been filed on the date on which they were substantiated. Since the respondent only provided the missing substantiation in its letter of 18 June 2024, admittance of the auxiliary requests must be assessed under Article 13(2) RPBA, which requires that any amendment to a party's appeal case after notification of a summons to oral proceedings is, in principle, not to be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned. The board considers that none of the respondent's arguments establishes the existence of exceptional circumstances justified by cogent reasons that would justify admittance of these requests at this late stage, and accordingly decides not to admit any of them into the appeal proceedings.

30. Moreover, the board notes that these auxiliary requests merely differ from the corresponding auxiliary requests 2b to 7b in that paragraph [0066] of the description was deleted and / or typographical corrections have been made to the claims. All these auxiliary requests are thus *prima facie* also not allowable because none of

them overcome the inventive step objection raised above.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

A. Vottner T. Sommerfeld

Decision electronically authenticated