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Datasheet for the decision of 11 April 2018

Case Number: T 0115/13 - 3.3.01

Application Number: 00928851.5

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Language of the proceedings: EN

Title of invention:

PROTEINS EXPRESSED BY MYCOBACTERIUM TUBERCULOSIS AND NOT BY BCG AND THEIR USE AS DIAGNOSTIC REAGENTS AND VACCINES

Patent Proprietor:

Rutgers, the State University of New Jersey

Opponents:

GlaxoSmithKline Biologicals SA
Statens Serum Institut

Headword:

Discriminatory diagnosis of tuberculosis/RUTGERS

Relevant legal provisions:
EPC R. 115(2)
RPBA Art. 15(3), 12(2), 12(4), 13(1)
EPC Art. 56

Keyword:
Summons to oral proceedings - non-attendance of party
Late-filed evidence
Late-filed request - submitted with the statement of grounds of appeal
Inventive step - (no)

Decisions cited:
G 0009/92, G 0007/93

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0115/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 11 April 2018

Appellant: (Patent Proprietor)	Rutgers, the State University of New Jersey Old Queen's Somerset Street New Brunswick, NJ 08909 (US)
Representative:	J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Party as of right: (Opponent 1)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Jenkinson, Kay Elizabeth GlaxoSmithKline 980 Great West Road Brentford, Middlesex, TW8 9GS (GB)
Party as of right: (Opponent 2)	Statens Serum Institut Artillerivej 5 2300 Copenhagen S (DK)
Representative:	Plougmann Vingtoft a/s Rued Langgaards Vej 8 2300 Copenhagen S (DK)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 13 November 2012 concerning maintenance of European patent No. 1214088 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	T. Sommerfeld
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 1 214 088, based on European patent application No. 00928851.5, which was filed as an international patent application published as WO 2000/066157, was granted with 13 claims.

II. Two oppositions were filed against the granted patent, both opponents requesting its revocation in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC, in conjunction with Article 100(a) EPC), insufficient disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. By an interlocutory decision announced at oral proceedings, the opposition division decided that the patent could be maintained in amended form on the basis of the second auxiliary request filed during those oral proceedings on 11 September 2012 (Articles 101(3)(a) and 106(2) EPC).

The opposition division considered that the claims according to the main request and to the first auxiliary request (both filed during the oral proceedings) lacked inventive step.

IV. The patent proprietor lodged an appeal against that decision. In its statement of grounds of appeal, it requested that the decision be set aside and that the patent be maintained on the basis of the main request, or alternatively according to the first or the second auxiliary request, all as filed with the grounds of appeal. The second auxiliary request was the same as the claims maintained by the opposition division.

V. Opponent 1 also lodged an appeal against the opposition division's decision. In its statement of grounds of appeal, it requested that the decision be set aside and the patent revoked in its entirety. It submitted new documents, D34 and D36 to D44 (numbering according to the consolidated list of the patent proprietor).

VI. Both appellants submitted replies to each other's grounds of appeal. With those replies, both dated 12 August 2013, the patent proprietor submitted new auxiliary requests (third to ninth) and a new document (D45), and opponent 1 submitted new documents (now numbered D46 to D50). The patent proprietor submitted a reply to opponent 1's reply.

VII. The parties were summoned to oral proceedings before the board scheduled for 11 April 2018.

VIII. By letter dated 23 January 2018, opponent 1 withdrew its appeal and announced that it would not attend the oral proceedings. The patent proprietor, now the sole appellant, filed further submissions by letter dated 9 March 2018, accompanied by new documents, D51 and D52.

IX. Opponent 2 (party as of right) filed a letter dated 27 March 2018, requesting that the appeal be dismissed, and that D51 and D52, as well as the first, fourth, seventh and ninth auxiliary requests, not be admitted into the proceedings.

X. Oral proceedings before the board took place on 11 April 2018. As it had announced in writing, opponent 1 did not attend.

During the oral proceedings, the appellant's third auxiliary request became its first auxiliary request, the previous first auxiliary request becoming the new second auxiliary request. At the end of the oral proceedings, the chairman announced the board's decision.

XI. The **main request** differs from the claims as granted in that claims 12 and 13 have been deleted. Claim 1 reads as follows:

"1. An *in vitro* method of diagnosis which discriminates between exposure of a subject to *Mycobacterium tuberculosis* (*M. tuberculosis*) and exposure of a subject to the Bacille Calmette Guerin strain of *Mycobacterium bovis* (BCG), the method comprising testing a population of cells from a subject for the presence of CD4 T lymphocytes that respond to MTBN4, as depicted in Figure 1, wherein the presence of CD4 T lymphocytes that respond to MTBN4 indicates that the subject has been exposed to *M. tuberculosis* and not to BCG without exposure to *M. tuberculosis*."

The **first auxiliary request** differs from the main request in that claim 1 is restricted to "a human subject".

In the **second auxiliary request**, claim 11 has been deleted and claim 1 has been amended as follows:

"1. An *in vitro* method of diagnosis which discriminates between exposure of a subject to *Mycobacterium tuberculosis* (*M. tuberculosis*) and exposure of a subject to the Bacille Calmette Guerin strain of *Mycobacterium bovis* (BCG), the method comprising testing a population of cells from a subject for the

presence of CD4 T lymphocytes that respond to MTBN4 as depicted in Figure 1 (or functional segment thereof) present within a composition, wherein the presence of CD4 T lymphocytes that respond to ~~MTBN4~~ said composition indicates that the subject has been exposed to *M. tuberculosis* and not to BCG without exposure to *M. tuberculosis*, further wherein said composition does not contain other *M. tuberculosis* polypeptides (or functional segments thereof)."

The **third auxiliary request** consists of the claims as maintained by the opposition division.

XII. The documents cited during the proceedings before the opposition division and the board include the following:

D3 WO 98/44119
D6 Mahairas G. et al. 1996, *J. Bacteriol.*, 1274-82
D10 WO 99/04005
D11 WO 98/16646
D21 Declaration by Dr Fletcher
D22 Elhay M. et al. 1998, *Infection and Immunity*, 3454-3456
D23 Weldingh K. et al. 1999, *FEMS Immunol. & Medical Microbiology*, 23, 159-164
D24 WO 00/26248
D25 Pathan A. et al. 1998, 10th International Congress on Immunology 1-6 November, abstract
D26 Olsen A. et al. 1998, 10th International Congress on Immunology 1-6 November, abstract
D27 Ulrichs T. et al. 1998, *Eur. J. Immunol.*, 28, 3949-3958
D28 Lyashchenko K. et al. 1998, *Infection & Immunity*, 66(11), 5344-5349
D29 Lyashchenko K. et al. 1998, *Infection & Immunity*,

66(8), 3936-3940

D30 Wilkinson R. et al. 1997, *J. Clin. Microbiol.* 35(3), 553-557

D31 Berthet F.-X., 1997, doctoral thesis and related articles

D34 CV of Prof. Andersen

D35 WO 99/24577

D36 Declaration by Prof. Andersen

D37 Espitia C. et al. 1991, *Arch. Invest. Med. (Mex)*, 22(1), 101-107

D38 Espitia C. et al. 1989, *Clin. Exp. Immunol.* 77, 373-377

D39 Brock I. et al. 2001, *Int. J. Tuberc. Lung Dis.* 5(5), 462-467

D40 Brock I. et al. 2004, *J. Clin. Microb.* 42(6), 2379-2387

D41 Streeton J. et al. 1998, *Int. J. Tuberc. Lung Dis.*, 2(6), 443-450

D42 Mori T. et al. 2004, *Am. J. Respir. Crit. Care Med.*, 170, 59-64

D43 Brusasca P. et al. 2001, *Scand. J. Immunol.*, 54, 448-452

D44 Weldingh K. et al. 2005, *J. Clin. Microb.* 43(1), 57-65

D45 Health Protection Agency, Information Sheet re: M Bovis Infection, June 2013

D46 Email from J Rothel to P Vostrup

D47 The Immunologist 1998, Supplem. 1, Abstracts of the 10th International Congress on Immunology, New Delhi, 1-6 November 1998, pp.440-441 (D25b)

D48 Declaration by A. Olsen (D26b)

D49 Library catalogue extract for D31 (D31b)

D50 Declaration by F.-X. Berthet about D31 (D31c)

D51 Declaration of Dr Gicquel

D52 Second declaration of Dr Fletcher

XIII. The appellant's submissions, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of late-filed documents

D24 to D31 had all been filed allegedly in response to D21, only a few days before the first-instance oral proceedings, and included a long doctoral thesis in French (D31). These documents were, however, not a reaction to D21 but instead to issues arising from the granted claims and could, therefore, have been filed earlier. Some of these documents were not even relevant, and in fact the opponent had attempted to rely only on D30, which, however, had not been admitted by the opposition division. As to D31, the date on which it had become publicly available was not clear, D49 and D50 not being convincing evidence. Moreover D31 was not even mentioned in the appealed decision. D35 was an intermediate document but was evidence of what the skilled person would have done at the effective date, namely of how the authors of D3 had pursued their work. Documents D47 to D50 were not to be admitted as they related to documents D26, D27 and D31, which were not to be admitted either. As to D51 and D52, they related to D10, which was a crucial document in the proceedings; they provided evidence of how D10 would have been interpreted by the skilled person at the relevant date.

Main request - inventive step

Starting from D22, the problem was to provide an alternative discriminatory assay. D22 itself suggested, on page 3455, right column, looking for other antigens, in particular in the deleted regions of the BCG genome,

to supplement the ESAT-6/MPT64 combination. It did not provide any suggestion to use CFP10. From D6, figure 2, the skilled person would be faced with a large number of antigens to investigate. D3 also looked for discriminatory reagents and disclosed excellent candidates in the RD1 region which the skilled person would further investigate; CFP10 was not one of them. The skilled person would not combine D22 with D10, which did disclose CFP10, because D10 was not directed to providing discriminatory assays, the context of Example 8 being vaccine development since the skilled person would construe it in accordance with the rest of D10's teaching; only an *ex post facto* analysis would suggest the combination. There was no mention of cell-mediated assays in D10, the mention of T-cell reactivity on page 3 being in relation to the prior art. Moreover, example 5 of D11 (page 53 and table 10 on page 54) would teach away from using CFP10/TB38-1 as a discriminatory antigen, since it showed that there was an immunological reaction to this antigen among the "healthy" patients too; such a positive reaction would be interpreted as likely to be due to BCG immunisation.

First auxiliary request - inventive step

D22 disclosed guinea pig, not human, data, and it could not be assumed that human and guinea pig immune systems were identical. Hence there was no expectation of success starting from D22. Although D22 suggested that the guinea pig model was suitable for humans, this was only in the context of DTH responses and not of *in vitro* testing. As to D10, the cellular-based assay was also obtained with guinea pigs, while the human data did not give any indication of what assay was used. Although the patent also used guinea pig data, this

data supported the claims in view of the patent's disclosure as a whole.

Second auxiliary request - admissibility

This request had been submitted in response to opponent 1's very late-filed documents and therefore could not have been filed earlier.

XIV. The opponents' arguments, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of late-filed documents

Documents D24 to D30 were a response to D21, in which the appellant's expert raised totally new issues. Document D31, the thesis, was *prima facie* highly relevant as it clearly pointed to using LHP/CFP10 in an assay. Document D35 was late-filed and not relevant and the content had not been publicly available at the relevant date. Document D36 too was a response to the appellant's expert. It could not have been filed earlier. Documents D51 and D52 were about the content of document D10, a document which had been in the proceedings from the start, and therefore documents D51 and D52 could have been filed at an earlier stage.

Main request - inventive step

D22 was not the most promising springboard for inventive step; instead D6, D3 or D10 was. MPT64, used in D22, was not discriminatory for all BCG strains (page 3455, right column, lines 7 to 11), as was also apparent from D6, page 1281, left column, third full

paragraph. Hence, D22's method was not entirely discriminatory. If D22 were taken as the closest prior art, the technical problem could be formulated as the provision of a truly discriminatory assay, since the claim was not restricted to certain BCG strains. Starting from D22, which disclosed ESAT-6 in the RD1 region, the skilled person would look for more antigens expressed in the same region and would therefore combine D22 with D10. The introductory part of D10 indicated that CFP10 was part of RD1 and the experiments of Example 8 would definitely be interpreted as meaning that CFP10 would be able to discriminate, which was what was required by D22. Although it was true that D10's focus was on vaccine development, it also referred to diagnostic methods, as specified, for example, in the sentence bridging pages 2 and 3.

First auxiliary request - inventive step

The restriction to humans did not contribute to inventive step. In the patent, data obtained with a guinea pig model had been extrapolated to humans, so the same could be done with D22 or D10, the latter even including human data. The guinea pig model was a generally accepted one for developing diagnostic agents for tuberculosis, the ultimate aim being, of course, to use them in humans: D22, page 3454, left column, second full paragraph, last 3 lines. The DTH response measured in D22 was based on T-cell response, so was in fact the *in vivo* version of the claimed *in vitro* test.

Second auxiliary request - admissibility

During the first instance proceedings, the patentee had opted not to submit amendments until the oral

proceedings. This request, which could have also been filed before the opposition division, had been filed as late as with the grounds of appeal and had never been assessed by the opposition division, meaning that its admission would be likely to require remittal to the opposition division.

XV. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, submitted with the letter of 25 March 2013, on the basis of auxiliary request 1 (former auxiliary request 3), submitted with the letter of 12 August 2013, or on the basis of auxiliary request 2 (former auxiliary request 1), submitted with the letter of 25 March 2013.

Opponent 1 (party as of right) had requested in writing, in its capacity as appellant, that the decision under appeal be set aside and the patent revoked, that the board confirm that document D35 had been excluded from the proceedings and that (former) auxiliary request 1 (now auxiliary request 2) be excluded from the proceedings. Opponent 1 did not file any new requests after withdrawing its appeal.

Opponent 2 (party as of right) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Prohibition of *reformatio in peius*

2.1 When opponent 1 withdrew its appeal, the patent proprietor became the sole appellant. According to decision G 9/92 of the Enlarged Board of Appeal (OJ EPO 1994, 875), if the patent proprietor is the sole appellant against an interlocutory decision maintaining a patent in amended form, neither the board nor the non-appealing opponent as a party to the proceedings as of right under Article 107, second sentence, EPC, may challenge the maintenance of the patent as amended in accordance with the interlocutory decision. As a consequence, the board needs to consider only the main request and auxiliary requests 1 and 2.

3. Absence of party as of right at the oral proceedings

3.1 The oral proceedings before the board took place in the absence of opponent 1, party to the proceedings as of right (Article 107 EPC), which had been duly summoned but decided not to attend.

3.2 According to Rule 115(2) EPC, if a party duly summoned to oral proceedings does not appear as summoned, the proceedings may continue without that party. Under Article 15(3) RPBA, the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying on its written case.

4. Admission of late-filed documents

4.1 Admission of late-filed documents in appeal proceedings is governed by the Rules of Procedure of the Boards of Appeal. According to Article 12(2) RPBA, the statement of the grounds of appeal and the reply thereto must

contain a party's complete case. Moreover, pursuant to Article 12(4) RPBA, it is at the board's discretion to admit evidence which could have been presented or was not admitted in the first-instance proceedings. When exercising its discretion, the board takes into account the circumstances of the particular case and the arguments put forward by the parties. Lastly, Article 13(1) RPBA leaves it to the board's discretion to admit any amendment to a party's case after it has filed its grounds of appeal. This discretion is to be exercised in view of, *inter alia*, the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy.

4.2 The board decided to admit documents D24 to D29, D35, D36 with exhibits, D47 and D48 into the proceedings, for the following reasons:

4.2.1 D24 to D29 were filed during the first-instance proceedings, prior to the oral proceedings. Although they were filed just a few days before the oral proceedings, their submission was a reaction to the new documents, D21 to D23, filed by the patent proprietor also just before the oral proceedings. Documents D47 and D48 were submitted with opponent 1's reply to the patentee's statement of grounds of appeal as evidence of the public availability of documents D25 and D26, in view of the patentee's doubts in this regard. Hence the board decided to admit these documents into the proceedings (Article 12(4) RPBA).

4.2.2 Contrary to opponent 1's statement in its reply to the patentee's grounds of appeal (section 2.3 on page 2), D35 was not excluded from the proceedings before the opposition division. Although an intermediate document, D35 was filed by the patent proprietor during the

first-instance proceedings as a reaction to opponent 1's very late-filed documents. The board thus does not see any reason not to admit this document into the proceedings. D35 was thus admitted into the proceedings (Article 12(4) RPBA).

4.2.3 Opponent 1 filed document D36 and exhibits with its grounds of appeal, as a reaction to the opposition division's decision. The appellant objected to their admission at the oral proceedings, but did not substantiate its objection, referring only to its written submissions (where no objection had been raised). Hence the board decided to admit these documents into the proceedings (Article 12(4) RPBA).

4.3 The board decided not to admit late-filed documents D30, D31 and D49 to D52 into the proceedings for the following reasons:

4.3.1 D30 was filed just before the first-instance oral proceedings and the opposition division decided not to admit it (sections 9.1 and 9.2 of the appealed decision). If the department of first instance takes a discretionary decision not to admit a document, it is not the function of the board to review all the facts and circumstances of the case, as if it were that first-instance department, in order to decide whether or not it would have exercised such discretion in the same way. A board should only overrule the way in which the first-instance department has exercised its discretion if it comes to the conclusion either that the first-instance department, in its decision, has not exercised its discretion in accordance with the right principles or that it has exercised its discretion in an unreasonable way, and has thus exceeded the proper limits of its discretion (G 7/93, OJ EPO 1994, 775,

Reasons, 2.6). None of the opponents provided arguments as to why the opposition division's decision not to admit this document was wrong in the sense mentioned above. The board thus saw no reason to overrule the opposition division's decision to exclude D30 from the proceedings. Accordingly, D30 was not admitted into the proceedings (Article 12(4) RPBA).

4.3.2 Opponent 1 filed D31 shortly before the first-instance oral proceedings, allegedly as a reaction to the late-filed documents D21 to D23. However, opponent 1 has made no reference to any particular part of this 229-page document, which includes a doctoral thesis in French and articles in English, instead just mentioning it as one piece of evidence that "at the priority date many were already working to further develop CFP10 based diagnostics" (letter of 4 September 2012, page 6, last two lines of the first paragraph). D31 was not discussed at all in the decision, nor was it mentioned during the appeal proceedings up to the oral proceedings. Thus, although opponent 2 contended, for the first time at the oral proceedings, that a very relevant passage in this document had been so far overlooked by all the parties, the board considered that any objections raised on the basis of specific passages in this document would necessarily constitute a fresh case. Therefore, the board decided to make use of its power under Article 12(4) RPBA not to admit this document into the proceedings. Since document D31 was not admitted into the proceedings, D49 and D50, which were filed by opponent 1 with its letter of reply to patentee's grounds of appeal as evidence of the date on which D31 had become publicly available, were also not admitted into the proceedings (Article 12(4) RPBA).

4.3.3 Documents D51 and D52 are expert declarations which were filed after the summons to oral proceedings had been issued, in fact just one month before the oral proceedings. The appellant did not give any explanation as to why these documents, which concern the interpretation of document D10, could not have been filed earlier. The board thus decided not to admit D51 and D52 into the proceedings (Article 13(1) RPBA).

5. Main request - inventive step

5.1 The patent discloses the invention as being "based on the inventor's discovery that a polypeptide encoded by an open reading frame (ORF) in the genome of *M. tuberculosis* that is absent from the genome of the Bacille Calmette Guerin (BCG) strain of *M. bovis* elicited a delayed-type hypersensitivity response in animals infected with *M. tuberculosis* but not in animals sensitized with BCG. Thus proteins encoded by ORFs present in the genome of *M. tuberculosis* but absent from the genome of BCG represent reagents that are useful in discriminating between *M. tuberculosis* and BCG and, in particular, for diagnostic methods (e.g., skin tests and *in vitro* assays for *M. tuberculosis*-specific antibodies and lymphocyte responsiveness) which discriminate between exposure of a subject to *M. tuberculosis* and vaccination with BCG. Thus, the present invention relates to *in vitro* methods of diagnosis which discriminate between exposure of a subject to *M. tuberculosis* and exposure of a subject to BCG." (paragraph [0003]).

5.2 As argued by the appellant, document D22, which is also directed to methods of tuberculosis diagnosis which enable distinction between infection with M. tuberculosis and sensitisation by M. bovis BCG

(abstract), is considered to be the closest prior art. The difference from the claimed subject-matter is two-fold, namely: D22 does not disclose an *in vitro* test, but an *in vivo* test (skin test); and D22 tests reactivity to different antigens, namely ESAT-6 and MPT64. There is no evidence or indication in the patent or elsewhere on file that the method as claimed is an improvement on that of D22, and hence the technical problem can be formulated as the provision of an alternative method for discriminating between infection with M. tuberculosis and vaccination with BCG; this was also how the appellant formulated the technical problem. In view of the data presented in the patent, the board is satisfied that the problem is solved by the claimed solution.

5.3 It next has to be decided whether the skilled person would arrive at the claimed solution in an obvious way.

5.4 Document D22 discusses the need for a tuberculosis species-specific reagent that "should distinguish vaccinated individuals or individuals exposed to environmental mycobacteria from patients infected with *Mycobacterium tuberculosis*" (page 3454, left column, first paragraph, last 4 lines). Two extracellular antigens from M. tuberculosis, ESAT-6 and MPT64, were known to be "recognised by T cells in animal models of TB [tuberculosis] and by human TB patients" and to be "found primarily in *M. tuberculosis* but not in most experimental mycobacteria or in BCG", and thus D22 proposes further investigating their "diagnostic potential" (page 3454, left column, second paragraph). Making use of a guinea pig model to study *in vivo* delayed-type hypersensitivity (DTH) responses (skin test) elicited by these antigens in animals exposed to M. tuberculosis or to BCG, D22 is able to show that

"ESAT-6 and MPT64 discriminate TB infection from BCG vaccination or exposure to environmental mycobacteria" (legend to FIG. 1). On page 3455, right column, D22 discusses the possible need for further M. tuberculosis-specific antigens: "The ultimate diagnostic reagent will possibly require other *M. tuberculosis*-specific antigens to cover all members of a genetically diverse population". It also states that such new antigens should be looked for in regions deleted from the BCG genome, in particular the regions that include the *esat-6* and the *mpt64* genes: "In this regard, a recent analysis of the regions deleted from the BCG genome during its generation and subsequent propagation has identified open reading frames that may encode antigens with diagnostic potential (11). One of the deleted regions includes the putative bovine *esat-6* gene, and a second region codes for *mpt64*. Characterization of these regions and cloning of antigens may yield reagents that could supplement the ESAT6-MPT64 combination in the future". Reference (11) mentioned in this passage is document D6 in the proceedings.

5.5 The skilled person, explicitly prompted by D22 to look for antigens in the BCG-deleted regions which include the *esat-6* and the *mpt64* genes, would thus turn to documents disclosing M. tuberculosis polypeptides, and in particular antigens in the said specific regions. One such document would be D10, which discloses "a new antigenic protein from Mycobacterium tuberculosis", designated LHP (page 3, line 22), but also referred as "CFP-10" (page 1, lines 12 to 13) and encoded by "a polynucleotide carrying the regulatory expression signals of the ESAT-6 protein" (page 3, lines 20 to 23). The cloned new polynucleotide is further disclosed in D10 as containing "a whole operon consisting in a

regulatory region containing a functional promoter and a functional ribosome binding site that drives the expression of two structural genes respectively encoding a new polypeptide named LHP and an already known polypeptide named ESAT-6", both structural genes being "co-transcribed under the control of the said promoter region" (page 12, lines 11 to 16). Also in the experimental part, D10 explicitly discloses that "*lhp* is next to *esat-6*" (page 54, line 16). So there can be no doubt that the antigenic polypeptide disclosed in D10 is part of the region that also encodes ESAT-6 and hence is, according to D22, a candidate reagent for an M. tuberculosis species-specific diagnostic test. The skilled person would then carefully consider the experimental data given in D10 in relation to this new antigenic protein, and in particular the immunological data disclosed in Example 8. Example 8 describes that CFP10 (another designation for the LHP protein) was tested in guinea pigs "on BCG vaccinated, M. avium and M. tub [tuberculosis] infected and naive animals" and states: "In BCG vaccinated, M. avium infected and naive animals no DTH response was measured compared to M. tub infected w[h]ere a significant DTH response was observed" (page 55, lines 16 to 22). Example 8 additionally states: "In human only TB infected but not BCG vaccinated donors respond to CFP10" (page 56, lines 1 and 2). Accordingly, Example 8 of D10 clearly teaches that the CFP10 protein coded by the newly cloned gene *lhp* enables immunological discrimination between M. tuberculosis infection and BCG vaccination.

5.6 The skilled person would thus be motivated to further pursue the diagnostic use of D10's CFP10 as an antigen enabling discrimination between M. tuberculosis infection and BCG vaccination and, based on the data of D10, would have a high expectation of success. Since

the amino acid sequence of D10's CFP10 differs from the MTBN4 amino acid sequence depicted in Figure 1 of the patent by only a single conservative amino acid substitution (Gly11Ala), the two polypeptides would elicit a response from the same CD4 T lymphocyte population, as was stated in the appealed decision (section 3.4) and not disputed by any of the parties. Moreover it was not disputed that testing for such a response using CFP10 instead of MTBN4 would fall within the ambit of claim 1.

5.7 As to the use of an *in vitro* method as claimed, instead of *in vivo* methods as disclosed in the closest prior art, D22, the following is noted: As argued by the opponents and not disputed by the appellant, the two tests are in fact two formats which assess exactly the same immunological response, namely CD4 T lymphocyte response. Moreover, D22 also referred to *in vitro* testing, on page 3455, right column, lines 3 to 5: "TB patients in a study in Kuwait responded to ESAT-6 and produced high amounts of gamma interferon to this antigen"; production of gamma interferon is one of the parameters that can be tested *in vitro* to assess CD4 T lymphocyte response, as is apparent from claim 6 of the main request. Lastly, the patent itself only presents *in vivo* data (skin testing) from a guinea pig model, and hence exactly the same experimental setting as disclosed in D22 and D10, to support claims directed to *in vitro* methods.

5.8 The board thus comes to the conclusion that the subject-matter of claim 1 lacks inventive step over the disclosures of D22 and D10.

5.9 The appellant essentially argued that D22 taught away from using a different discriminating antigen, and

instead suggested adding further antigens to the disclosed ESAT-6/MPT64 combination. Moreover, the skilled person would not combine the teachings of D22 with those of D10, because D10 would not be read in the context of diagnostic assays but only in the context of vaccine development. Instead, the skilled person would turn to D3, which disclosed a number of antigens that were deleted in BCG, and would not further investigate CFP10 as a discriminatory antigen. Moreover, the skilled person would be taught away from using CFP10 by the results of Example 5 of D11.

5.10 As regards D22's suggestion to supplement the ESAT6/MPT64 combination (page 3455, right column, last four lines), the board notes that the present claims do not exclude the use of further antigens in the test together with the MTBN4 antigen. D22 clearly suggests investigating further discriminating antigens in the M. tuberculosis genome regions that are deleted in the BCG genome and, just by following this suggestion, the skilled person would arrive at the *lhp* gene-encoded protein CFP10, as discussed above, used alone or in an ESAT6/MPT64 combination. As to document D10, it is true that this document is mainly related to vaccine development. However, it also specifically refers to diagnosis as one of the purposes of the invention disclosed, for example on page 3, lines 14 to 16: "[T]here is a great need in the art of suitable protein expression systems allowing the preparation of mycobacterial immunogenic polypeptides that are useful for diagnostic and vaccine purposes" (emphasis added by the board). In this context, it is noted that, even if D10's main purpose might have been to identify virulent determinants of M. tuberculosis, the approach underlying that purpose was in fact to detect those antigens which were deleted from non-virulent strains,

i.e. BCG strains, and thus basically the same approach as mentioned in D22 with the aim of identifying discriminating antigens; clearly, nothing impedes antigens from being used for both purposes. Indeed D10, while discussing D6's identification of three regions of difference between virulent M. bovis and the attenuated M. bovis strain BCG, states: "RD1 was detected in all strains of M. tuberculosis and M. bovis tested but is absent in all BCG substrains, suggesting that it may be an important determinant of virulence" (page 2, lines 18 to 20). Hence, proteins encoded by genes deleted from the BCG genome are, according to D10, potential virulence determinants; likewise, D22 teaches that genes deleted from the BCG genome are candidates for use as discriminatory reagents. The skilled person would thus assume that potential virulence antigens are also potential discriminatory antigens.

5.11 Moreover, the fact that D3 identified other potential discriminatory antigens is not in itself evidence that CFP10 was not deemed interesting, or that the skilled person would not look for further antigens. As to D11's Example 5, the board disagrees that its results would teach away from using the Tb38-1 antigen tested (which differs from the MTBN4 claimed in that it lacks five amino acids at the N-terminus; appealed decision, section 3.11). These results suffer from the problem that it is not entirely apparent how the test subject groups were defined, in particular the "healthy patients"; most importantly, there is no information at all concerning their BCG vaccination status, and hence it is not possible to draw relevant conclusions as regards the discriminatory ability of the Tb38-1 antigen tested.

5.12 The main request is thus not allowable because it does not comply with Article 56 EPC.

6. First auxiliary request - inventive step

6.1 Claim 1 of this request differs from claim 1 of the main request merely in that it is restricted to human subjects. The board considers that this limitation does not contribute to inventive step. In fact D22, albeit using a guinea pig model, also clearly aims at developing discriminatory diagnostic methods for use in humans, and the skilled person would have no reason to doubt that the data obtained for the guinea pig model could be extrapolated to humans. There would also be no reason to doubt that the *in vivo* results obtained in D22 would translate into the same *in vitro* results. In fact, the patent itself uses the same guinea pig model and the same *in vivo* tests to support claims directed to *in vitro* testing of humans. Moreover, D10 also specifically discloses a discriminatory immune response to CFP10 in humans (page 56, lines 1 and 2); although it is not clear what test (*in vitro* or *in vivo*) was used in these human experiments, it is nevertheless clearly stated that there was an immune response for M. tuberculosis-infected patients and no response for BCG-vaccinated individuals.

6.2 The first auxiliary request is therefore also not allowable because it lacks inventive step (Article 56 EPC).

7. Second auxiliary request - admissibility

7.1 Appeal proceedings are intended to review the correctness of first-instance decisions, not to

continue examination by other means. Thus, pursuant to Article 12(4) RPBA, it is at the discretion of the boards of appeal to admit requests which could have been presented in the proceedings before the examining or opposition division, account being taken of the circumstances of the particular case and of the parties' arguments.

7.2 The second auxiliary request was filed as the first auxiliary request with the statement of grounds of appeal. In this request, claim 1 contains amendments that had not been submitted in any of the requests filed during the first-instance proceedings.

7.3 According to the appellant, the amendments in the first auxiliary request were made as a response to opponent 1's very late-filed documents D26 to D30. The opponents objected to this request's admission on the ground that it introduced subject-matter which had never been examined by the opposition division and its admission might therefore require remittal of the case to the department of first instance.

7.4 The board notes that opponent 1's very late-filed documents had in fact not been used at all in the reasoning for the opposition division's decision. The board fails to see how a request which is filed by the appellant with the statement of grounds of appeal as a reaction to documents filed by the other party but which were not found relevant for the appealed decision can serve as a means to redress the appealed decision. Hence, the board makes use of its discretionary power under Article 12(4) RPBA and decides not to admit the second auxiliary request into the proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated