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Datasheet for the decision of 13 December 2011

Case Number: T 0146/07 - 3.3.08

Application Number: 98910845.1

Publication Number: 0994963

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Non-invasive prenatal diagnosis

Patentee:
ISIS INNOVATION LIMITED

Opponent:
Ravgen Inc.

Headword:
Prenatal diagnosis/ISIS

Relevant legal provisions:
EPC Art. 56, 83, 87, 115
EPC R. 50(3), 86, 114(1)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Anonymous third party observations (deemed not to have been filed)"
"Sufficiency of disclosure (yes)"
"Priority (valid)"
"Inventive step (yes)"

Decisions cited:
G 0002/98, G 0001/03, G 0002/03, T 0735/04

Catchword:
See points 3 to 6 of the Reasons

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0146/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 13 December 2011

Appellant: (Opponent)	Ravgen Inc. 9241 Rumsey Road Columbia, MD 21045 (US)
Representative:	Brasnett, Adrian Hugh Mewburn Ellis LLP 33 Gutter Lane London EC2V 8AS (GB)
Respondent: (Patent Proprietor)	ISIS INNOVATION LIMITED Ewert House Ewert Place Summertown Oxford OX2 7SG (GB)
Representative:	Roques, Sarah Elizabeth J.A. Kemp & Co. 14 South Square Gray's Inn London WC1R 5JJ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 19 December 2006 concerning maintenance of European patent No. 0994963 in amended form.**

Composition of the Board:

Chairman: R. Moufang
Members: M. R. Vega Laso
T. J. H. Mennessier

Summary of Facts and Submissions

I. European patent No. 0 994 963 with the title "Non-invasive prenatal diagnosis" was granted on European patent application No. 98910845.1 (published as WO 98/039474).

II. The patent, which was granted with 21 claims, was opposed on the grounds for opposition mentioned in Article 100(a) and (b) EPC 1973, in particular that the claimed subject-matter lacked an inventive step (Article 56 EPC 1973), and that the claimed invention was not sufficiently disclosed in the patent. In connection with the objection of lack of inventive step, the opponent questioned the validity of the priority in respect of the invention in claims 1 and 15 to 19.

III. In an interlocutory decision under Articles 102(3) and 106(3) EPC 1973 posted on 19 December 2006, the opposition division decided that the invention in claim 1 of the main request (claims 1 to 20 filed with letter of 19 July 2006 as auxiliary request 1) had not been sufficiently disclosed, contrary to Article 83 EPC 1973. However, the amended claims according to auxiliary request 1 (claims 1 to 19 filed at the oral proceedings before the opposition division) and the invention to which they related, were considered to fulfil all requirements of the EPC. The opposition division thus decided that the patent could be maintained on the basis of these claims and an adapted description filed also at the oral proceedings.

IV. Independent claim 1 and dependent claims 14 to 17 according to auxiliary request 1 read:

"1. A detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample, wherein said nucleic acid is a paternally inherited sequence which is not possessed by said pregnant female.

14. A method according to claim 12 or 13, for the detection of a maternal or foetal condition in which the level of foetal DNA in the maternal serum or plasma is higher or lower than normal.

15. A method according to claim 14, for the detection of pre-eclampsia.

16. A method according to claim 14, for the detection of a foetal chromosomal aneuploidy.

17. A method according to claim 16, wherein said foetal chromosomal aneuploidy is Down's syndrome."

Dependent claims 2 to 13 concerned various embodiments of the method of claim 1. Claims 18 and 19 related to a method of performing a prenatal diagnosis, using the method of any one of claims 1 to 17.

V. The opponent (appellant) lodged an appeal against the interlocutory decision of the opposition division and requested the revocation of the patent. As a subsidiary request, oral proceedings were requested. Together with the statement of grounds of appeal, the appellant filed a consolidated list of documents and additional documentary evidence.

VI. The proprietor (respondent) submitted observations on the grounds of appeal and requested, *inter alia*, oral proceedings.

VII. The parties were summoned to oral proceedings on 20 January 2011. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the board expressed its provisional opinion on some of the issues to be discussed during the oral proceedings, in particular issues concerning sufficiency of disclosure (Article 83 EPC), priority (Article 87 EPC 1973) and inventive step (Article 56 EPC 1973).

VIII. The appellant informed the board that it would not be represented at the scheduled oral proceedings, and withdrew its request for oral proceedings. The respondent filed a reply to the board's communication and put forward arguments supporting an inventive step, in particular with regard to a combination of documents (14) and (15).

IX. On 10 January 2011, the parties were informed by telefax that the board had decided to cancel the oral proceedings and take a decision on the basis of the written submissions.

X. On 18 January 2011, observations by an anonymous third party were received. A copy of the observations was forwarded to the respondent under Rule 114(2) EPC.

XI. On 24 February 2011, the respondent submitted comments on the anonymous observations.

XII. In the present decision, the board refers to the following documents:

(1): Douglas et al., November 1959, Am. J. Obst. & Gynec., Vol. 78, No. 5, pages 963 to 973;

(2): J. Walknowska et al., 7 June 1969, The Lancet, pages 1119 to 1122;

(6): L. Raptis and H. A. Menard, December 1980, J. Clin. Invest., Vol. 66, pages 1391 to 1399;

(9): S. Strickland and W. G. Richards, 30 October 1992, Cell, Vol. 71, pages 355 to 357;

(10): M. Martin et al., 1992, Human Immunology, Vol. 33, pages 108 to 113;

(11): S. L. Emanuel and S. Pestka, 1993, GATA, Vol. 10, No. 6, pages 144 to 146;

(13): J. L. Simpson and S. Elias, 1994, Prenatal Diagnosis, Vol. 14, pages 1229 to 1242;

(14): Y.-M. D. Lo et al., 1994, British Journal of Haematology, Vol. 87, pages 658 to 660;

(15): K. R. Fowke et al., 1995, Journal of Immunological Methods, Vol. 180, pages 45 to 51;

(17): H. E. Mulcahy et al., 7 September 1996, The Lancet, Vol. 348, page 628;

(19): Y. M. D. Lo et al., 16 August 1997, The Lancet, Vol. 350, pages 485 to 487;

(21): W. Holzgreve and S. Hahn, 2000, Baillière's Clinical Obstetrics and Gynaecology, Vol. 14, No. 4, pages 709 to 722;

(23): B. Pertl and D. W. Bianchi, September 2001, Obstetrics & Gynecology, Vol. 98, No. 3, pages 483 to 490;

(26): B. M. Byrne et al., 2003, Hypertens Pregnancy, Vol. 22, No. 2, pages 157 to 164;

(30): Y. M. D. Lo et al., 1999, Clinical Chemistry, Vol. 45, No. 10, pages 1747 to 1751;

(31): Y. M. D. Lo et al., 1999, Clinical Chemistry, Vol. 45, No. 2, pages 184 to 188.

XIII. The submissions made by the appellant in writing, as far as they are relevant to this decision, may be summarized as follows:

Article 83 EPC - Claims 14 to 17

Claims 14 to 17 lacked an enabling disclosure. It was not possible in a single sample from an individual female to know what was "normal" for that individual and whether the amount of DNA detected was lower or higher than normal. The patent did not teach what was meant by "normal". Moreover, it was apparent from Figures 1 and 2 of the patent in suit that there was no specific "normal" foetal DNA value for a pregnant woman.

As concerned the methods of claims 15 to 17, it was suggested in documents (19), (26) and (23) published after the priority date of the patent in suit that pre-eclampsia or foetal chromosomal aneuploidy, in particular trisomy 21, could not be detected using the claimed methods. It was stated in document (19) - a scientific publication co-authored by the inventors of the patent in suit - that a method as claimed in claim 1 "might" be suitable for the diagnosis of aneuploidies, "if" there was a quantitative difference in foetal DNA concentration in these conditions. It was clear from this statement that, even after the priority date, the inventors did not know whether or not Down's syndrome could be diagnosed by their method. Thus, they could not have been able to teach in the application as filed how to perform such a diagnosis. The data in Figure 1 of the patent merely confirmed that the method could not be used for the diagnosis of aneuploidy.

As regards the diagnosis of pre-eclampsia, it was concluded from the results of a much larger study published in document (26) that the differences in foetal DNA concentration between women suffering from pre-eclampsia and control women were not statistically significant. Furthermore, no correlation was found between the quantity of foetal DNA and disease severity.

In document (23), the "considerable degree of overlap" between foetal DNA concentrations in women carrying trisomy 21 and euploid male foetuses was discussed. The authors concluded that, due to the relatively low sensitivity and specificity of the measurement of circulating foetal DNA, a combination with other

markers for foetal trisomy 21 was needed. Additionally, DNA markers that would identify female foetuses with Down's syndrome were said to be needed, because at the time only gene sequences from the Y chromosome were used as basis of detection. It could be derived from document (23) that only a very specific and unusual trisomy originating in a chromosomal rearrangement of paternal DNA would be detectable by the technique disclosed in the patent. A classical trisomy comprising a single additional whole chromosome would not be detectable.

The suggestion in paragraph [0018] of the patent in suit that the detection of trisomy 21 might be possible by quantitating the relative amount of chromosome 21 DNA compared to other foetal DNA appeared extremely speculative. No proof had been provided that either of the two ways suggested in the patent would work. The statements in the patent were a mere "hope" to succeed. Furthermore, in the case of a trisomy in which two copies of the maternal chromosome 21 were present, it would not be possible to use the methodology of the patent to determine the ratio of this chromosome to other foetal chromosomes, because the total additional amount of chromosome 21 DNA in the plasma was not detectable.

If there were serious doubts - supported by verifiable facts - that the patent lacked an enabling disclosure, the burden of proof should be placed on the patent proprietor. In the present case, the post-published documents (19), (26) and (23) indicated that it was not possible to practice the invention claimed in claims 16 and 17 in the manner suggested in the patent for the

detection of trisomy. Moreover, there were technical considerations suggesting that diagnosis of trisomy would not be feasible from foetal DNA analysis alone.

Article 87 EPC - Priority - Claims 14 to 17

Claim 14 and claims 15 to 17 depending therefrom were not entitled to the priority date and, consequently, document (19) was prior art to be considered for the assessment of inventive step.

Claim 14 related to a detection method in which the level of foetal DNA in the maternal serum or plasma was "higher or lower than normal". This meant that the level of DNA had to be determined and compared to a reference level, i.e. one which was normal. The priority application did not teach this. On page 2, lines 24 to 27 of the priority application it was stated that the inventors claimed "detection and monitoring of pregnancy-associated conditions such as pre-eclampsia which may result in differing amounts of foetal DNA being present in the maternal serum or plasma". No reference standard for "differing" was given. Since "differing" could be interpreted as "differing over the course of time" or "differing from an undefined threshold (as opposite to average)" or even "differing from a previous pregnancy in the same mother", the term could not be considered as a direct and unambiguous disclosure of "differing from normal".

According to G 2/98 (OJ EPO 2001, 413), the test for priority was a strict one. If, after the filing of the priority application, a third party had filed an application setting out the subject-matter of claim 15

or claim 16, those claims would clearly belong to that third party. For a valid priority, it was not enough to have a priority document containing a teaching which, on a possible construction, encompassed the subject-matter of a later claim.

Article 56 EPC - Inventive step

For the assessment whether or not the method of claim 1 involved an inventive step, there were two alternative approaches starting with two different strands of art. Both approaches were equally valid and led to the same conclusion, i.e. that claim 1 did not meet the requirements of Article 56 EPC.

In one approach, the relevant prior art was document (14) in the light of document (15). Document (14) related to the detection of foetal DNA sequences in the buffy coat fraction isolated from maternal peripheral blood. This fraction contained both foetal and maternal white blood cells. Document (15) taught that the DNA isolation technique described in document (14) presented a problem in the processing time and the use of caustic chemicals. It also taught that, instead of buffy coat, a serum or plasma sample could be used to determine HLA genotypes, using PCR amplification of DNA present in the sample. It was clear from this document as well as from documents (6), (11) and (10) that by 1997 the presence of DNA in circulating human blood was well established. It had also been recognised that this DNA originated from different cellular sources, including but not limited to peripheral blood cells. Accordingly, the skilled person reading document (15) in the light of

document (14) had every incentive to detect foetal DNA sequences directly from plasma.

Moreover, he/she had more than a reasonable expectation of success. This could be seen from document (13), in which the isolation of foetal cells in maternal blood for prenatal diagnosis was reviewed. The statements in this document were consistent with the disclosure of document (2). Thus, having regard to documents (14) and (13), it would have been a surprise for a person skilled in the art *not* to find foetal DNA in maternal plasma.

An alternative and equally valid starting point for the assessment of inventive step was to consider the prior art relating to other forms of foetal cells in the maternal circulation, particularly the trophoblast. At the priority date it was known that migration of trophoblastic cells into the maternal blood stream was a normal process of pregnancy (see documents (1) and (13)). The similarities between embryonic implantation and tumour metastasis were discussed in document (9), and in document (17) it was reported that DNA from tumour cells was found in the plasma of cancer patients.

Starting from document (14), the problem to be solved was to provide an alternative source of DNA to the buffy coat fraction. In view of document (13), it was an obvious alternative to isolate DNA from trophoblastic cells present in maternal blood. Since document (17) taught that cells with invasive tendencies, of which trophoblasts were a well known type, could be detected by analysis of plasma, it was

obvious to look at plasma in the expectation that it would contain trophoblast DNA.

XIV. The submissions made by the respondent, as far as they are relevant to this decision, may be summarized as follows:

Observations by an anonymous third party

The third party observations should be disregarded by the board since they were filed anonymously and at a very late stage of the proceedings.

Article 83 EPC - Claims 14 to 17

The requirement of Article 83 EPC was met in respect of claims 14 to 17 because the claimed invention could be reproduced and had been reproduced by those skilled in the art. It had not been demonstrated that the invention could not be carried out based on the teaching of the specification.

By comparing the level of foetal nucleic acid in a sample taken from the mother to the level in samples taken previously from the same woman or, alternatively, to reference samples, a person skilled in the art could establish whether or not the level of foetal nucleic acid in a sample was lower or higher than normal.

The documents cited by the appellant demonstrated that the methods claimed in claims 14 to 17 were useful in the diagnosis of aneuploidy and pre-eclampsia. The authors of document (26) established that the median SRY copy number was greater in women with pre-eclampsia,

and document (23) demonstrated that there were detectable differences in the levels of foetal nucleic acid in, e.g., pre-eclampsia and Down's syndrome. While the latter document made reference to low sensitivity and specificity for Down's syndrome, that did not mean that the technique did not work, but merely that further optimisation might be required in order to enhance specificity and sensitivity. Document (23) reported that an abnormally strong signal from DNA sequences present on chromosome 21 was detected, which was consistent with the fact that three copies of this chromosome were carried by foetuses having Down's syndrome.

Article 87 EPC - Priority - Claims 14 to 17

Claim 14 was entitled to priority because the priority application taught detecting and monitoring pregnancy-associated conditions such as pre-eclampsia which may result in differing amounts of foetal nucleic acid being present in the maternal serum or plasma. The detection of pre-eclampsia, foetal chromosomal aneuploidy and Down's syndrome was specifically referred to in the priority document. Thus, also for claims 15 to 17, the relevant date was the priority date.

Article 56 EPC - Inventive step

Document (14), which could be regarded as the closest prior art, described the extraction of nucleic acid from the cellular fraction of maternal blood and its subsequent analysis using the polymerase chain reaction to detect foetal sequences. There was, however, no

suggestion that plasma or serum should or even could be used for the detection of foetal sequences.

Even though the presence of circulating nucleic acid in the serum or plasma of healthy patients had been known for some years before the priority date, the source of the nucleic acid had not been recognised. The fact that a particular cell type was found to be circulating in blood did not necessarily mean that also nucleic acid from those cells would be present in blood in detectable amounts. None of documents (6), (11) and (17) showed that for any cells circulating in blood, associated DNA could be found.

There was no evidence on file that the foetal cells circulating in blood had the same properties as maternal peripheral blood mononuclear cells. As discussed in document (13), there were a number of different foetal cell types circulating in maternal blood. The fact that, at the priority date, nucleic acid could be detected and analysed in serum or plasma from healthy individuals did not provide any teaching to assist one of skill in the art in establishing whether foetal nucleic acid could also be detected in maternal plasma or serum. Furthermore, it was neither taught nor suggested in the documents on file that the detection rate was much higher using serum or plasma than using nucleated blood cells extracted from a comparable volume of whole blood.

As concerned the appellant's second line of argument, the relevant disclosure in document (13) was the suggestion that trophoblasts circulating in maternal blood could be isolated for subsequent analysis of

their nucleic acid. The problem to be solved could be formulated as the provision of an alternative method for the detection of foetal nucleic acid. The solution provided in the patent was not obvious, either having regard to document (13) alone or a combination of documents (13) and (17). While document (9) suggested that there were some similarities between tumour cells and trophoblasts, the similarities related to enzymes involved in invasion or implantation. Since there were also many differences between trophoblasts and cancer cells, it was not possible for one of skill in the art to expect that any characteristic of cancer cells would also be found for foetal cells.

Thus, the claimed methods involved an inventive step within the meaning of Article 56 EPC. Documents (21), (23), (24) and (25) demonstrated that the claimed invention was considered to be a significant development in the field.

XV. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

XVI. The respondent (patent proprietor) requested that the appeal be dismissed.

Reasons for the Decision

Procedural issues

1. The opponent is the sole appellant against the interlocutory decision of the opposition division, which held that the patent could be maintained in

amended form on the basis of the claims according to the auxiliary request 1 filed at the oral proceedings and a description adapted thereto.

2. The appellant contested the decision under appeal only in respect of the findings on sufficiency of disclosure (Article 83 EPC 1973), validity of the priority (Article 87 EPC 1973) and inventive step (Article 56 EPC 1973) concerning the set of claims according to auxiliary request 1. The appellant did not raise any objections to the opposition division's findings concerning Rule 57a and Articles 123(2)(3) and 84 EPC 1973, and the board sees no reason to raise any objections of its own motion in this respect.

3. Anonymous third party observations were received by the board at a very late stage, i.e. after the scheduled oral proceedings had already been cancelled in view of appellant's announcement not to attend these proceedings and the withdrawal of its subsidiary request for oral proceedings (see paragraphs VIII to X above). According to Rule 114(1) EPC, any observations by a third party shall be filed in writing. This requirement implies that the observations have to be signed (see Rules 50(3) and 86 EPC) in order to allow an identification of the third party (see Schachenmann in: Singer/Stauder, Europäisches Patentübereinkommen, 5th ed., Art. 115 marg. no. 13). Identification is particularly important in the context of opposition proceedings in order to allow the competent organ of the EPO to verify whether the observations are indeed filed by a third party rather than by a party to the proceedings. Otherwise, a party might be tempted to submit late observations and/or documents by means of

anonymous third party observations in order to avoid negative procedural consequences such as apportionment of costs.

4. When a party to the proceedings submits an unsigned document, the document is deemed not to have been filed if, after a corresponding invitation has been sent out by the EPO, it is not signed in due time (see Rule 50(3) EPC). Since unsigned anonymous third party observations do not allow the EPO to send out such an invitation at all, they necessarily remain unsigned. This has the consequence that they are deemed not to have been filed.

5. The board is aware that anonymously filed third party observations may nevertheless be adopted by a party to the proceedings as its own or may even trigger objections by the competent organ of the EPO of its own motion (see decision T 735/04 of 13 September 2007, point 2 of the reasons, dealing with the exceptional situation that a highly relevant patent application of one of the patent proprietors had been submitted by an anonymous third party). However, in the absence of such a further procedural act, anonymous third party observations are to be disregarded altogether. This view is in line with the decisions G 1/03 and G 2/03 (OJ EPO 2004, 413 and 448) in which the Enlarged Board of Appeal refused to take into account an anonymously filed third party statement (see Section VI(3) of the decisions).

6. Thus, the anonymous observations under Article 115 EPC received on 18 January 2011 are deemed not to have been filed and are disregarded by the board.

Sufficiency of disclosure (Article 83 EPC) - Claims 14 to 17

7. In the decision under appeal, the issue of sufficiency of disclosure was decided in connection with claims 1 and 15 to 17 of the main request. Even though there is no explicit finding in the decision concerning the set of claims according to auxiliary request 1, the board infers from the opposition division's finding that the patent could be maintained on the basis of these claims, that the requirement of Article 83 EPC 1973 was considered to be met.

8. In the reasons given for the decision on the main request, the opposition division regarded the results shown in Figures 1 and 2 of the patent in suit and in documents (30) and (31) as conclusive evidence that, in spite of the high number of false negatives and the low quality of the detection, the invention still allowed the detection of at least some pregnant females suffering from pre-eclampsia or carrying foetuses affected by chromosomal aneuploidy. Consequently, the opposition division decided that the methods of claims 15 to 17, as far as they concerned the detection of paternally inherited nucleic acid sequences which differed from the sequences of the corresponding maternal DNA, conformed to Article 83 EPC 1973.

9. Claims 14 to 16 of auxiliary request 1 are - except for the amended dependencies - identical to claims 15 to 17 of the main request. Thus, the opposition division's findings on the latter claims apply, *mutatis mutandis*, to the corresponding claims 14 to 16 of auxiliary request 1. In its statement of grounds of appeal, the appellant contended that the invention claimed in

claims 14 to 17 of auxiliary request 1 could not be carried out by a person skilled in the art. The appellant, however, did not submit any specific counter-arguments against the reasons given by the opposition division in connection with the main request. Rather, as concerned claim 14 it argued that, since there was no specific "normal" foetal DNA value for a pregnant woman, it was impossible to determine what constituted a value which was "higher than" or "lower than" normal, as required in present claim 14 (see paragraph XIII above).

10. This argument fails to persuade the board. The fact that no cut-off value for DNA in plasma or serum is disclosed in the application as filed in connection with the diagnosis of pre-eclampsia or the detection of chromosomal aneuploidies - including trisomy 21 - does not, in the board's view, mean that such a value cannot be determined applying statistical methods which are well-known in the field of diagnostic tests. A skilled person working in this field at the relevant date knew that "normal" or cut-off values for a particular marker can be determined in large-scale studies comparing affected and unaffected pregnancies, and that statistical analysis of the data obtained may be required. In its communication under Article 15(1) RPBA, the board expressed the provisional view that the data acquisition and analysis required for determining cut-off values were routine work which would neither require inventive skills nor put an undue burden on the skilled person. No arguments or evidence which contradict the board's view have been submitted by the appellant.

11. In its statement of grounds of appeal, the appellant pursued further the objection raised in opposition proceedings that the patent in suit did not teach a person skilled in the art how to perform the diagnosis of Down's syndrome. As evidence in support of this objection, the appellant relied on documents (19), (26) and (23), which were published after the priority date of the patent in suit.

12. The board is unable to derive from document (19) any verifiable facts supporting the objection raised by the appellant. Contrary to the appellant's view, the statement made by the authors in the passage on page 487 of document (19) ("*... if there is a quantitative difference ...*") must not necessarily be understood as an expression of uncertainty. The board interprets this passage as generally pointing to the fact that quantitative differences are required in order for chromosomal aneuploidies to be detected.

13. As concerns document (26), the board observes that the analysis described therein was carried out on the basis of the DNA extracted from maternal peripheral **blood**, which means that not only DNA in maternal plasma but also DNA from circulating foetal cells was determined. Thus, the analysis in document (26) is based on a method which is different from the method claimed in the patent and, consequently, any results obtained or any conclusions drawn from this analysis are not necessarily valid for the method of claim 15. Furthermore, the board observes that the conclusion drawn by the authors from the reported experiments points to a lack of correlation between the amount of DNA in peripheral blood and disease **severity**. This

cannot be considered as conclusive evidence that detection of pre-eclampsia by analysis of the amount of DNA in serum or plasma is not feasible.

14. Finally, the statements in the passages of document (23) on which the appellant relied in support for its objection of lack of sufficient disclosure of the methods according to claims 16 or 17, do not cast, in the board's judgement, serious doubts concerning the feasibility of the claimed method for detecting foetal chromosomal aneuploidy, in particular Down's syndrome. The passage on page 487 of document (23) to which the appellant pointed (see paragraph bridging the left- and right-hand columns) indicates that a better sensitivity and specificity can be achieved by combining the measurement of circulating foetal DNA with other markers for foetal trisomy 21. This passage cannot, in the board's view, be construed to mean that the methods of the invention as such may not allow screening for Down's syndrome.

15. Moreover, contrary to the appellant's argument, there is no statement in document (23) to the effect that foetal genes suitable for screening female foetuses have (yet) to be identified. Rather, the remark in the last sentence of the paragraph is understood by the board as indicating that, since gene sequences from the Y chromosome were used as basis of detection at that time, for female foetuses with Down's syndrome to be identified applying a method as claimed, other DNA markers must be used. See in this respect also the last sentence under the heading "RESULTS" in the summary on page 483 of document (23), stating that screening tests for Down's syndrome, pre-eclampsia or preterm labour

"... ***currently*** *rely on the detection of Y chromosomal sequences and consequently are limited* ***presently*** *to male fetuses*" (emphasis in bold added by the board).

16. For the reasons given above, documents (19), (26) and (23) cannot be regarded as conclusive evidence that the invention in claims 15 to 17 cannot be carried out by a person skilled in the art without an undue burden of experimentation.

17. In its statement of grounds of appeal, the appellant admitted that two different methods of detecting Down's syndrome were suggested in the application as filed (see the passage on page 5, lines 3 to 26 of the application which corresponds to paragraph [0018] of the patent). Nevertheless, the appellant argued that in the absence of experimental evidence the burden of proof that either method worked must be shifted to the respondent.

18. The board does not share this view. There is no evidence on file which supports the appellant's contention that a person skilled in the art applying either method suggested in the passage on page 5 of the application as filed would not be able to detect foetal chromosomal aneuploidies, in particular trisomy 21. The fact that in the documents cited by the appellant - which were published after the priority date of the patent in suit - the approaches suggested in the application as filed were not followed, does not necessarily mean that a person skilled in the art could not carry out the invention claimed in claim 17 using those methods. Since, in the board's judgement, the arguments put forward by the appellant either in

opposition or in appeal proceedings fail to raise serious doubts as to the sufficiency of the disclosure concerning the methods of claims 15 to 17, the burden of proof is not shifted to the respondent, but rests with the appellant.

19. Having considered the arguments and evidence on file, the board concludes that the objection of lack of sufficient disclosure raised by the appellant is not justified.

Article 87 EPC 1973 - Priority - Claims 14 to 17

20. In the decision under appeal, the opposition division found concerning the invention in claims 1, 12, 13 and 14 that the priority claimed in the patent was valid and that, consequently, the relevant date for determining whether or not a document formed part of the state of the art within the meaning of Article 54(2) EPC 1973 was 4 March 1997.

21. While the appellant did not contest the opposition division's findings on claims 1, 12 and 13, it disputed that the passage on page 2, lines 19 to 29 of the priority document described the same invention as in claim 14. In particular, it argued that the term "differing" could be interpreted in different manners and, therefore, could not be regarded as a clear and unambiguous disclosure of the feature "higher or lower than normal" in the context of claim 14 (see paragraph XIII above).

22. The board does not share this view. Even though the term "differing" as such could in fact be given

different meanings, in the context of the passage on page 2 of the priority application the sole possible interpretation is "differing from the normal", which is tantamount to "higher or lower than normal". It is stated in the priority application that molecular monitoring of an abnormal medical condition such as pre-eclampsia, in which, as a result of placental damage, alterations in foetal DNA concentration in maternal serum and plasma are likely, could be performed by accurate quantitation of foetal nucleic acid levels in the maternal serum or plasma (see paragraph bridging pages 5 and 6 of the priority application). In the board's judgement, a person skilled in the art reading this passage of the priority application understands immediately that an **alteration** of the foetal DNA level can only be determined by comparison to the normal level, i.e. to the expected level as determined by statistical analysis of normal pregnancies. As stated by the opposition division in its decision, it is not the quantification of a certain parameter but rather the comparison to what is considered "normal" that leads to a diagnosis (see point 6.3 of the decision under appeal). This was certainly within the general knowledge of the skilled person at the relevant date.

23. The board thus concludes that the invention in claim 14 was disclosed in the priority application, and that the priority right in this respect has been validly claimed.

24. Consequently, document (19) does not form part of the state of the art.

Article 56 EPC - Inventive step

25. In the decision under appeal, the opposition division found that a skilled person, starting from document (14) as the closest prior art and confronted with the problem of providing a method for detecting foetal nucleic acids with higher sensitivity, would not derive the solution proposed in claim 1 from document (15). Consequently, the subject-matter of claim 1 was considered to involve an inventive step within the meaning of Article 56 EPC 1973.

26. On appeal, the parties agreed that document (14), which describes a method for the detection of foetal RhD sequences in **peripheral blood** of sensitized RhD-negative pregnant women, represents the closest state of the art. In the method described in document (14), antecubital venous blood was collected from pregnant women and DNA was extracted from the buffy coat fraction. Foetal RhD sequences were detected by PCR using specific primers.

27. In the view of the opposition division, the method described in document (14) differs from the method of claim 1 in that the presence of nucleic acid of foetal origin is detected in "buffy coat", i.e. peripheral blood mononuclear **cells** (PBMC) isolated from maternal peripheral blood, rather than in maternal serum or plasma as specified in claim 1. This finding was not contested by the appellant. In fact, for the isolation of PBMC as described in document (14), the plasma must be discarded.

28. However, in its statement of grounds of appeal the appellant questioned the opposition division's findings as regards the technical problem to be solved. The appellant submitted that, having regard to document (14), the technical problem the skilled person was confronted with had to be formulated as providing an alternative source of foetal nucleic acid. In the appellant's view, the solution proposed in claim 1, i.e. the use of a maternal plasma or serum sample instead of buffy coat for the detection of foetal nucleic acid, was obvious to a person skilled in the art at the relevant date.

29. The appellant put forward two alternative lines of argument. In its first line of argument, the appellant maintained that the drawbacks of the method described in document (14) - longer processing time and use of caustic chemicals - were apparent from document (15), in which the substitution of the buffy coat fraction with the plasma fraction was suggested. A person skilled in the art reading document (15) in the light of document (14) had, in the appellant's view, every incentive to detect foetal DNA sequences directly from plasma.

30. The board disagrees with this view. As stated above, document (14) relates to a method in which a cellular fraction of maternal blood is analysed for foetal DNA. There is no suggestion in this document that foetal DNA can be detected in a maternal sample other than a cellular fraction. The sole suggestion provided in document (14) is to improve the accuracy of the assay by using specific foetal cell enrichment strategies, such as those for nucleated red cells or for

trophoblasts (see document (14), page 660, left column, last paragraph). Thus, a person skilled in the art reading this document had a motivation to use such enriched cellular fractions as an alternative source of foetal nucleic acid. A motivation to look for circulating, cell-free foetal nucleic acid in serum or plasma samples of maternal blood is, however, not apparent to the board.

31. Document (15), on which the appellant further relied, relates to the analysis of circulating nucleic acid in serum or plasma. As the respondent argued, the fact that circulating nucleic acid is present in the blood of an individual had been known for many years before the relevant date of the patent. Although different sources of such circulating nucleic acid had been suggested in the literature (see documents (6), (11) and (17), there was no conclusive evidence as to where the nucleic acid originated. Neither was there an indication in the literature - at least not in any of the documents cited by the appellant - that circulating **foetal** nucleic acid might be present in maternal blood.

32. Under these circumstances, the board judges that it would not have been obvious to a person skilled in the art, having regard to document (14), either alone or in combination with document (15), to try to detect a nucleic acid of foetal origin which is paternally inherited in maternal serum or plasma, as proposed in claim 1.

33. In a second line of argument, the appellant contended that it was known in the art that DNA from cancer cells can be found circulating freely in the blood of cancer

patients - document (17) was cited as evidence in this respect -, and that trophoblastic cells can be found in maternal blood. In the appellant's view, the many close analogies between tumour growth and trophoblast invasion of the maternal uterus described in document (9) would lead a person skilled in the art to consider extending the analogy to the detection of DNA in serum or plasma.

34. In the board's judgement, the appellant's reasoning is tainted by hindsight. Document (9) does not point to any analogies whatsoever between tumour and trophoblast cells, but rather to analogies between two **processes**: on the one hand, the release of the unfertilized egg from the ovary, the transport of the embryo through the oviduct and uterus, and the implantation of the embryo; and, on the other hand, tumour cell metastasis. Albeit the authors of document (9) suggest that the enzymatic and cellular machinery necessary for the two processes may be related (see page 356, right column, first paragraph under the heading "Relevance of Implantation to Tumour Invasion and Metastasis"), the board considers that a person skilled in the art would not have drawn from this teaching the conclusion that foetal nucleic acid can be detected in maternal serum or plasma.

35. Summarising the above: in view of the evidence and arguments put forward by the appellant in its statement of grounds of appeal, the board is not persuaded that the method of claim 1 was obvious to a person skilled in the art at the relevant date. The same applies to the methods of claims 2 to 19. Thus, in the board's judgement, the opposition division's finding that the

claimed subject-matter involves an inventive step within the meaning of Article 56 EPC is correct.

36. Hence, none of the objections raised by the appellant prejudices the maintenance of the patent in amended form as decided by the opposition division.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski R. Moufang