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D E C I S I O N
of 6 November 2002

Case Number: T 0338/00 - 3.3.8

Application Number: 93900894.2

Publication Number: 0619842

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Language of the proceedings: EN

Title of invention:
Multimeric forms of members of the steroid/thyroid superfamily of receptors

Applicant:
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

Opponent:
-

Headword:
Multimeric Receptors/SALK INSTITUTE

Relevant legal provisions:
EPC Art. 52(1), 52(2), 57, 56, 82
EPC R. 27(1)(f), 30

Keyword:
"Main request - discovery (no)"
"Industrial application (yes)"
"Inventive step (no)"
"First auxiliary request - unity (no)"
"Second auxiliary request - inventive step (yes)"

Decisions cited:
G 0010/93, T 0119/82, T 0022/85, T 0116/85, T 0056/87, T 0060/89, T 0606/89, T 0455/91, T 0500/91, T 0187/93, T 0296/93, T 0298/93, T 0786/93, T 0207/94, T 0223/94, T 0115/96, T 0717/96, T 0333/97, T 0338/97, T 0800/99

Catchword:
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Case Number: T 0338/00 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 6 November 2002

Appellant: THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 21 October 1999 refusing European patent application No. 93 900 894.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julia
S. C. Perryman

Summary of Facts and Submissions

I. An appeal was lodged by the applicant (appellant) against the decision of the examining division issued on 21 October 1999 whereby the application No. 93 900 894.2 which was published as international application WO 93/11235 with the title "Multimeric forms of members of the steroid/thyroid superfamily of receptors", was refused pursuant to Article 97(1) EPC on grounds of lack of inventive step (Article 56 EPC).

II. The decision was based on a set of 18 claims filed on 13 February 1997, wherein independent claim 1 read as follows:

"1. A heterodimeric receptor comprising one member selected from isoforms of RXR and one different member of the steroid/thyroid superfamily of receptors."

Dependent claims 2 to 7 characterized the isoforms of RXR and the specific members of this steroid/thyroid superfamily of receptors. Independent claims 8 and 9 were concerned with the heterodimeric receptors of claim 1, wherein for one of the members only (at least) the dimerization domain was required. Independent claim 10 was directed to an in vitro method to modulate, in an expression system, the transcription activation of a gene by forming the heterodimeric receptors of claim 1. Dependent claims 11 to 18 were specific embodiments of claim 10 defining the gene and hormone response elements as well as the particular members of the heterodimeric receptor used in the expression system.

III. In the view of the examining division the claimed subject-matter was novel vis-à-vis the following documents:

D1: C.K. Glass et al., Cell, 1989, Vol. 59, 697-708;

D2: L.M. De Luca, FASEB J., 1991, Vol. 5, 2924-2933;

D3: R.M. Evans, Science, 1988, Vol. 240, 889-895;

D4: C.K. Glass et al., Cell, 1990, Vol. 63, 729-738;

D5: D.J. Mangelsdorf et al., Nature, 1990, Vol. 345, 224-229.

However, it lacked an inventive step having regard in particular to the combination of documents D1 and D2.

The examining division considered document D1 as the closest prior art. This document disclosed the existence of retinoic acid-thyroid hormone receptor heterodimers, namely RARα-TRβ, as well as in vitro methods to modulate the transcriptional activation of a gene by said heterodimers. Document D1 suggested that the interaction as observed between human RARα and human TRβ could also take place **with other and between other** members of the steroid/thyroid hormone receptor superfamily and novel patterns of gene expression were expected to result therefrom. Thus, the examining division considered that the technical problem underlying the present application was to verify the teachings of document D1. The claimed technical solution, namely RXR heterodimers, represented a specific selection among all possible members of the steroid/thyroid hormone receptor superfamily. However, **any** member of this superfamily - and without restriction - was a possible candidate in any presumptive heterodimer combination and the skilled person would have turned to any document providing information upon said members. Document D2, a general review in the field of retinoic acid research, referred in detail to the retinoic acid receptors RAR and RXR as

well as to their isoforms. The identification of RXR as a member of the steroid/thyroid hormone receptor superfamily was shown in document D5, which disclosed the cloning and partial characterization of said RXR. There was nothing in the prior art that would have hindered the skilled person to select RXR as the one member in the teachings of document D1. Therefore, and as far as all dependent claims were concerned with heterodimers of RXR with other known members of this superfamily, the examining division considered that none of the claims comprised any inventive subject matter.

IV. With the statement of grounds of appeal, the appellant submitted the following documents:

D6: T.H. Bugge et al., EMBO J., 1992, Vol. 11(2), 1409-1418;

D7: M. Pfahl, Skin Pharmacol., 1993, Vol. 6 (Suppl. 1), 8-16.

V. The board issued a communication pursuant to Article 11(2) of the rules of the procedure of the boards of appeal indicating with reference to decision G 10/93 (OJ EPO 1995, 172) that issues of Articles 52(1) and 57 EPC as well as Article 52(2)(a) EPC and Articles 84 EPC and 83 EPC needed also to be discussed and giving the board's preliminary, non-binding opinion on them.

VI. In reply to the board's communication, the appellant submitted written arguments concerning the issues of Articles 52(1) and 57 EPC as well as Article 52(2)(a) EPC and Articles 84 EPC and 83 EPC. Reference was made to the grounds of appeal for Article 56 EPC.

VII. Oral proceedings were held on 6 November 2002. During

oral proceedings the set of claims filed on the 13 February 1997 was maintained as appellant's main request (MR) and two auxiliary requests (AR-I and AR-II) were submitted to the board. Independent claim 1 of AR-I read as follows:

"1. A heterodimeric receptor comprising one member selected from isoforms of RXR and one different member of the steroid/thyroid superfamily of receptors selected from COUP-TF, PPAR, EAR-2 and VDR or another isoform of RXR than the first member."

Dependent claims 2 and 3 characterized the isoforms of RXR. Independent claims 4 and 5 corresponded to the dimers of claims 8 and 9 of the main request but restricted to the specific members of this AR-I. Independent claim 6 was concerned with the in vitro method of claim 10 of the main request but again restricted to the specific members of the AR-I. Dependent claims 7 to 11 were embodiments of claim 6 defining the gene and hormone response elements as well as the members of the heterodimeric receptor used in the expression system.

Independent claim 1 of AR-II read as follows:

"1. A heterodimeric receptor comprising one member selected from isoforms of RXR and COUP-TF."

Dependent claim 2 characterized the isoforms of RXR. Independent claims 3 and 4 corresponded to the dimers of claims 8 and 9 of the main request but restricted to the specific members of this AR-II. Independent claim 5 was concerned with the in vitro method of claim 10 of the main request but again restricted to the specific

members of the AR-II. Dependent claims 6 to 9 were embodiments of claim 5 defining the gene and hormone response elements used in the expression system.

VIII. The appellant's arguments and submissions on appeal may be summarized as follows:

Main request

In respect of **Article 52(a) EPC (discovery) and Articles 52(1) and 57 EPC (industrial application)**, the appellant referred to decision T 116/85 (OJ EPO 1989, 13) and to the established case law as supporting a broad interpretation of "industrial applicability". The disclosure of the present application not only demonstrated that the heterodimeric receptors were actually formed but that the transcription of genes maintained under expression control in the presence of a ligand was modulated. Moreover, it was known in the prior art that members of the steroid/thyroid hormone receptor superfamily and, more particularly of the retinoic acid receptor subfamily, exerted transcriptional regulation of various physiological processes. The information obtained by the present application was in so far of importance for the pharmaceutical industry because it could allow the design of more effective hormonal therapeutics. In this context the appellant submitted a letter showing license agreements with another commercial company.

In respect of **Article 56 EPC**, the appellant considered document D1 as the closest prior art. This document disclosed that **one, and only one**, pair of steroid/thyroid hormone receptors could form a functional heterodimer, namely the heterodimer RARα-TRβ. Two other steroid/thyroid hormone receptors, namely the α2 isoform of the human thyroid hormone receptor and the estrogen receptor, were not capable of

forming functional heterodimeric complexes with RARα. Starting from this closest prior art, the technical problem underlying the present application was defined as the provision of alternative combinatorial forms of at least two steroid/thyroid hormone receptors which could act cooperatively to regulate the transcription of gene sequences in cells in a manner different from the pattern of regulation observed by the transcription achieved by a homodimeric pair of a single steroid/thyroid hormone receptor as well as an in vitro method to modulate transcription using these heterodimeric receptor complexes. This technical problem was successfully solved by the heterodimeric RXR complexes and related subject matter disclosed in the application. The established case law with respect to the definition and attitude of the person skilled in the art had to be taken into account when considering the teachings of D1. In particular the appellant referred to T 500/91 (of 21 October 1992) and T 455/91 (of 20 June 1994) as defining the correct, cautious viewpoint of the skilled person, to T 296/93 (OJ EPO 1995, 627), T 187/93 (of 5 March 1997) and T 119/82 (OJ EPO 1984, 217) concerned with the reasonable expectation of success and the so-called "would/could" approach and to T 56/87 (OJ EPO 1990, 188), T 786/93 (of 30 January 1997), T 223/94 (of 16 February 1996), T 115/96 (of 25 February 1997) and T 717/96 (of 10 July 1997) as stating that the teaching of a prior art document had to be taken as a whole and it was not allowable to arbitrarily isolate parts thereof so as to derive technical information distinct from the teaching as a whole.

Following this established case law and in view of the failures shown in document D1, the skilled person would not have made a generalization of the specific interaction of the α form of the RAR and the β form of TR to a broad interaction of any forms of retinoic acid

receptor with any form of steroid/thyroid hormone receptors in general. The mechanisms by which these receptors exerted their effects on patterns of transcription were not known at the priority date and the skilled person could not have foreseen that they had interchangeable activities. Moreover, document D1 provided an explanation for the very selective interaction of the RARα and the TRβ, namely the importance of their C-terminal regions and more particularly their high degree of identity (53%) in this region. However, the relevance of other regions (such as the DNA binding domain), the effect of the ligands as well as the physiological environment surrounding these proteins were all emphasized in D1 as playing a major and unpredictable role for a successful interaction too.

These results were in line with other prior art. Document D2 recognized the extreme diversity in the RAR subfamily of receptors and it stressed that the C-terminal ends were important for receptor dimer formation. Document D2 referred to the family of retinoid receptors RXR which were said to have a very low homology with other RARs, being substantially different in primary structure and ligand specificity from the previously described RAR. The same information was conveyed by D5 which referred to RXR as functioning at the molecular level in a different manner than RAR. Document D5 explicitly stated that the putative ligand-binding domains (C-terminal regions) of RXR and RAR had a low degree of homology and that the comparison between the RAR subfamily and RXR revealed nothing to suggest that RXR was related to any of the known retinoid receptors. Thus, in view of this information, the skilled person would not have flown against the face of the combined teachings of document D1 and documents D2/D5. There could have been no reasonable expectation of success in applying the RXR heterodimers

for the teachings of document D1. Even though document D1 did not provide any instruction to investigate further, the skilled person could (but not would) then have cautiously investigated other closely related steroid/thyroid hormone receptors which had a greater homology at the C-terminus than RXR, such as for instance other known isoforms of the retinoic acid receptor RAR and/or the thyroid hormone receptor. Document D4 did not add anything of significance to this prior art as it failed to provide any concrete evidence for equating the RARα "coregulators" with "steroid/thyroid hormone receptor proteins", i.e. presence of "heterodimers". The appellant cited the post-published documents D6 and D7 as further evidence showing that the homodimerization was considered to be the general mechanism of the steroid/thyroid hormone receptor interaction whereas the heterodimerization disclosed in document D1 was seen as a particular anomaly.

In conclusion, the appellant argued that starting from document D1, the skilled person would not have selected a heterodimeric complex of the RXR protein and a further steroid/thyroid hormone receptor in order to solve the technical problem posed in the present application with an expectation of success, regardless of the teaching of any other cited prior art.

Auxiliary request I

All claims of this AR-I were directed or concerned with heterodimeric receptors with one member selected from the isoforms of RXR. The appellant considered that (i) the presence of RXR as a common member in all the heterodimeric receptors of claim 1 of this AR-I and mainly (ii) the very special functional and structural role played by said RXR member, as it was clearly shown in the post-published documents D6 and D7, were the

"special technical features" (Rule 30(1) EPC) which linked the claimed heterodimeric receptors and provided the single general inventive concept as required by Article 82 EPC.

Auxiliary request II

The selection and limitation of the claims to only one group of specific heterodimeric receptors overcame the objection for lack of unity raised for the AR-I. All claims of the AR-II were concerned with these specific heterodimeric RXR-COUP-TF receptors. None of the prior art documents on file anticipated this selection and there was no hint or suggestion in this prior art that could have led the skilled person to chose the claimed heterodimeric receptors in an obvious manner.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 18 as filed on 13 February 1997 (MR) or on the basis of claims 1 to 11 of the auxiliary request I filed at oral proceedings on 6 November 2002, or claims 1 to 9 of auxiliary request II and the amended description and drawings filed at the oral proceedings on 6 November 2002.

Reasons for the Decision

Main request
Article 52(2) EPC (discovery) and Articles 52(1) and 57 EPC (industrial applicability)

1. According to Article 52(1) EPC for a European patent to be granted an invention has to satisfy inter alia the requirement of being "susceptible of industrial application". Article 57 EPC indicates that an

invention is considered "as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture". Rule 27(1)(f) EPC prescribes that the description should indicate explicitly, when it is not obvious from the description or the nature of the invention, the way in which the invention is capable of exploitation in industry. Article 52 EPC gives in paragraph (2) (a)-(d) a non-exhaustive list of items which are not regarded as an invention. This includes "discoveries" in (a). All these items have in common that they refer to activities which do not aim at any direct technical result but are rather of an abstract and intellectual character (cf. T 22/85 OJ EPO 1990, 12).

2. In the present case the board felt it necessary to examine whether for the claimed heterodimeric receptor or dimer and for the claimed method to modulate transcription activation of a gene the way in which they are capable of being exploited in industry can be derived from the description or whether what is described is merely an interesting research result that might yield a yet to be identified industrial application. These questions are directly linked to the question whether the disclosed interaction of receptors to form heterodimers is a mere "discovery", i.e. the result of purely intellectual activity with no practical or technical character.

3. The board agrees with the appellant in that the present application not only discloses the presence of cooperative interactions to form heterodimeric receptors between the retinoic acid receptor RXR and other members of the steroid/thyroid hormone receptor hormone superfamily but provides also further evidence on the use of these heterodimers for modulating suitable transcription expression systems. References to the possible relevance of the disclosed heterodimers

in several physiological processes (development, differentiation and homeostasis) are explicitly found in the application too. Moreover, the application makes available an in vitro method for screening the suitability of other members of the steroid/thyroid hormone receptor superfamily to form heterodimers with RXR and, implicitly, its possible use to screen further compounds for their ability to modulate and/or to alter the disclosed cooperative interactions. The activities and products disclosed in the application are not aimed at an abstract or intellectual character but at a direct technical result that may clearly be applied in an industrial activity (modulation of the expression of a gene/product of interest in a particular expression system, screening of products with specific pharmacological activity, etc...). Thus, the board considers that the claimed subject matter fulfils the requirements of Article 57 EPC and Article 52(1) and (2) EPC.

Article 56 EPC (inventive step)

4. For objectively assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal consistently apply the "problem and solution approach", which requires as a first step the identification of the "closest prior art". In accordance with the established case law of the boards of appeal (cf. T 800/99 of 17 January 2001, T 606/89 of 18 September 1990), the "closest prior art" is generally that document which corresponds to a similar use or purpose and requires the minimum of structural and functional modifications. In the best case, that purpose should be something already mentioned in this

prior art document as a goal worth achieving (cf. T 298/93 of 19 December 1996). In the present case, the board agrees with both the appellant and the examining division in that document D1 represents the closest prior art to the claimed subject matter.

5. Document D1 discloses a heterodimer between two members of the steroid/thyroid hormone receptor superfamily, namely the human retinoic acid receptor RARα and the human thyroid hormone receptor TRβ. This RARα-TRβ heterodimer is detected by the functional cooperative interaction of both members on a subset of thyroid hormone response elements (TREs) (page 698, Figures 1c and 1d) and further evidence is provided by cross-linking experiments (page 699, Figure 2). Similar functional results are obtained with human RARα and rat α1 TR but not with human RARα and human α2 TR or estrogen receptor (page 699, right-column, lines 1-12 and Figure 1d on page 698). Using a series of deletion mutants, document D1 identifies both the ligand binding domain (ligand-BD) and the DNA binding domain (DNA-BD) as being required for the cooperative DNA binding of RARα and TRβ to the TREs (pages 700 to 701 and Figures 3 to 5). Document D1 refers to the dimerization interface and its importance for the cooperative interaction between both receptors. It is in this context that document D1 discloses a 34 amino acid region at the C-terminal domain of both receptors and their high degree of identity (53%) in this region (pages 701 and 704, Figure 4). Reference is made to the significant amphipathic character of this 34 amino acid region and the ability to form a coiled coil interaction with each other (page 701, left-column). The functional cooperativity between both receptors is further investigated through their transcriptional effects on two plasmids having different TREs and using firefly luciferase as a reporter gene (Figures 6 to 7 and pages 701 to 704). A possible model of their

functional interaction is shown in Figure 8 (page 705) and all these results are said to suggest that the thyroid hormone receptor and the retinoic acid receptor may interact to exert novel regulatory effects on the patterns of gene expression in several tissues (page 705, right-column, second sentence of the last full-paragraph).

Document D1 explicitly states that (i) "... (t)he observation that the thyroid hormone and retinoic acid receptors can functionally interact raises the possibility that **they** may also interact with other members of the steroid receptor gene superfamily, resulting in novel patterns of gene expression ..." (paragraph bridging pages 697-698) and (ii) "...(t)hese results suggest that by forming heterodimers, more elaborate control of transcription can be achieved by creating receptor combinations with differing activities ..." (page 697, abstract, last sentence) and "...(w)e speculate that interactions of the type described between the thyroid hormone and retinoic acid receptors may occur between other members of the ligand-dependent transcription gene family. Such interactions may be required to achieve the necessary complexity of transcriptional control that serves to regulate the processes of growth, development, and homeostasis" (page 706, last paragraph). The board understands these references as directed to two different types of possible heterodimers, namely (i) specific heterodimers which comprise either human RARα or TRβ with any other possible member of the steroid/thyroid hormone receptor superfamily, and (ii) general heterodimers comprising any possible member of the steroid/thyroid hormone receptor superfamily.

6. Starting from this closest prior art, the board considers that the objective technical problem underlying the present application must be seen in the

provision of alternative heterodimer receptors of the steroid/thyroid hormone receptor superfamily so as to broaden the range of available regulatory factors of gene transcription. The technical solution provided by the present application are the claimed heterodimeric receptors comprising one member selected from isoforms of RXR and another member of the steroid/thyroid superfamily of receptors. In view of the ability of the exemplified RXR heterodimers to specifically modulate the expression of a gene sequence through a thyroid hormone response element, the board is satisfied that the claimed solution solves the above mentioned technical problem.

7. Having regard to the explicit suggestions of document D1 (point 5 above), the board is convinced that it would have been obvious to the skilled person to follow these suggestions and try to obtain alternative heterodimer receptors. The skilled person, by choosing the first type of possible heterodimers suggested in document D1, namely the specific heterodimer receptors comprising either RARα or TRβ with other known members of the steroid/thyroid hormone receptor superfamily, would have adopted a conservative and cautious attitude in agreement with the criteria of the established case law cited by the appellant. The skilled person in question would neither have gone against any established prejudice nor have tried to enter into any unpredictable area (T 500/91 and T 455/91 supra).

In fact, document D1 not only speculates on the production of alternative heterodimer receptors but it actually exemplifies this suggestion by trying several known members of the steroid/thyroid hormone receptor superfamily, such as the rat α1 and the human α2 forms of the thyroid hormone receptor as well as the estrogen receptor. Thus, the board cannot concur with the appellant in that the skilled person would have

arbitrarily isolated parts of document D1 to derive information distinct from the teachings of the document as a whole (T 56/87, T 223/94, T 115/96 and T 717/96 supra) and it is convinced that the skilled person not only could have followed the more conservative suggestion of document D1 but that it would have actually followed it in view of the teachings of said document (T 119/82 supra).

8. Following the "conservative" suggestion of document D1, the skilled person would have been then faced with a great number of possible combinations between either RARα or TRβ and any other member of the steroid/thyroid hormone receptor superfamily. However, document D1 provides a clear guidance to narrow the number of these possible combinations. Document D1 not only emphasizes the importance of a 34 amino acid region within the C-terminus domain but it also discloses the amphipathic character of the cooperative (coiled coil) interaction and the relevance of the degree of identity in this region between both receptors (Figure 4, page 701). This teaching, which is in agreement with the general knowledge in the prior art (formation of homodimers), is further confirmed by the examples of document D1. Thus, whereas similar functional results than RARα and TRβ are obtained with RARα and rat TRα1 (closely structurally related to TRβ), no interaction is found with RARα and the estrogen receptor (less closely related to TRβ). The absence of any interaction between RARα and human TRα2 is also consistent with this criteria as said variant originates from an alternative splicing event which results in sequence divergence in this 34 amino acid region within the C-terminus domain (page 700, right-column, last paragraph).

As document D1 already discloses the ability to form heterodimers by closely related forms of one of those members (TRβ/TRα) and in order to further investigate the complexity of transcriptional control by these heterodimers, the skilled person would have followed the "conservative" suggestion of document D1 in a straightforward manner and it would have looked for members of the steroid/thyroid hormone receptor superfamily which (i) were less closely related forms than the ones exemplified in document D1 (so as to have a broader range of transcriptional effects and/or factors) but (ii) not so distantly related as the estrogen receptor (so as to be able to dimerize).

9. It is at this stage, looking for other members of the steroid/thyroid hormone receptor superfamily related to RARα or TRβ, that the selection of the retinoic acid RXR receptor would have been obvious to the skilled person. The importance of RAR in the retinoid pathway for controlling differentiation and development processes is well-known in the prior art as well as the presence and relevance of other retinoid-binding proteins in this pathway. However, apart from the α, β and γ forms of RAR and their isoforms, there is only one other nuclear retinoid receptor known, namely the RXR (document D2, Table 1). Even if RXR is substantially different in primary structure to RARα (document D5, abstract) and it has a low homology to RARα (document D2, page 2929 right-column, first full-paragraph) so as not to allow to be classified as a member of the RAR subfamily (RARα, RARβ, RARγ and their isoforms), both documents D2 and D5 explicitly compare the properties of these two types of nuclear retinoic acid receptors and they clearly identify RXR as a member of the steroid/thyroid hormone receptor superfamily having the characteristic structural domains and the ligand-dependent transcription activity of all members of this family. Document D5 further

refers to a potential difference in their ligand specificity (page 226, right-column) but without excluding that they could recognize chemically similar or identical molecules even if their ligand binding domains are only distantly related (page 228, right-column). Moreover and most importantly, the retinoic acid RXR receptor fulfils the selection criteria outlined in point 8 above, namely (i) to be less closely related to RARα than other RAR forms (broader range of transcriptional effects) and, however, (ii) not so distantly related as the estrogen receptor (ability to dimerize) (point 10 below).

10. In cases where the prior art provides incentives or suggestions to do something and it thus seems obvious for the skilled person to follow the indicated pathway, the question may arise whether the said skilled person, based on a scientific evaluation of the facts at hand, would thereby have had a "reasonable expectation of success" (cf. T 60/89 OJ EPO 1992, 268).

In agreement with the teachings of document D1, the expectation of success for obtaining heterodimers would have been directly dependent on the degree of identity between the C-terminal domains of both receptors and more particularly between the 34 amino acid region within these C-terminal domains as well as the conservation of the amphipathic character of this 34 amino acid region. According to Figure 2 of document D5, the C-terminal domains of the retinoic acid RXR and RARα receptors have a sequence identity of 27%, whereas document D1 refers to a sequence identity between the corresponding domains of RARα and TRβ of 34% (page 698, right column and Figure 1a). The degree of identity in the 34 amino acid region between RARα and TRβ is said to be 53% (document D1, page 701, left-column, second sentence), whereas a comparison of the corresponding sequence from RXR (document D5, Figure 1) and RARα

results in a value of about 30% with several conservative exchanges which do, however, maintain the amphipathic character of the interaction interface. As previously stated (point 8 above), such an intermediate degree of identity (between the higher degree of other known RAR or TR forms and the lower one of the distant estrogen receptor) would have been the one actually looked for by the skilled person. The board considers that, whereas a reasonable expectation of success is notoriously less likely to exist when a specific technical improvement is intended to be achieved, if what is looked for are only alternatives showing more or less the same effect as in the closest prior art, then the skilled person will follow up hints in the prior art which suggest already some likelihood of success in achieving this unambitious aim: success need not be certain. This is actually the situation of the present application, wherein any possible effect on the modulation of the transcriptional activity already solves the technical problem in a satisfactorily manner.

It is also established case law that the absence of particular expectations cannot be equated to an absence of a "reasonable expectation of success" (cf. T 333/97 of 5 October 2000) and that a "reasonable expectation of success" does not need to require (experimental) certainty (cf. T 338/97 of 7 February 2000).

11. It is in this context that the appellant has referred to several factors that would put in jeopardy this reasonable expectation of success. As stated for eg in T 207/94 (OJ EPO 1999, 273), in order to be considered, any allegation of factors putting in jeopardy the reasonable expectation of success must be based upon

technical facts. In the present case, however, none of the alleged factors would put off the skilled person from trying the RXR receptor and/or lower its expectations of success.

(i) According to the appellant document D1 refers to several regions (such as the DNA binding domain; page 700, right-column) or structural determinants as being involved in the cooperative interaction (page 704 right-column). There is no consistent effect of the ligand on the overlapping regions of the ligand binding domain and the dimerization interface (page 701, right column). However, these known facts do not actually put off the authors of document D1 from trying other members of the steroid/thyroid hormone receptor superfamily (rat TRα1 and human TRα2). Document D1 clearly emphasizes the importance of the C-terminus domain and more particularly of the 34 amino acid region within this domain, which is explicitly singled out in document D1 as being "essential" for the cooperative interaction (page 704, right-column). The results and failures obtained in document D1 are satisfactorily explained and fully in agreement with the relevance of this "essential" 34 amino acid region.

(ii) The applicant has referred to the importance of the physiological environment surrounding these proteins as well as to the fact that the mechanisms by which these receptors exert their effects on patterns of gene transcription were not known at the priority date. However, this deficiency is not remedied by the present application. The present disclosure does not allow the skilled person to predict with certainty the specific effect on the pattern of

gene transcription for each possible heterodimer comprising the RXR receptor, let alone the possible influence of the physiological environment on said effect. This effect, namely a positive or negative modulation of the transcription, has still to be experimentally determined for each one of the claimed heterodimers. The model of the interaction proposed in Figure 8 of document D1 is fully in agreement with the general one predicted for members of the steroid/thyroid hormone receptor superfamily and it is confirmed by both the examples of document D1 and the ones of the present application.

(iii) The board cannot concur with the appellant in that the authors of document D4 were very reluctant to conclude that the phenomenon observed (regulation of RARα by multiple cell-type specific proteins) was caused by "heterodimers". The authors of document D4 explicitly favour the presence of distinct heterodimers over complexes containing at least three proteins (page 735 paragraph bridging left to right-column) and, in view of the similar (i) molecular weight, (ii) DNA-binding properties and (iii) sequences involved in the interface domain, the authors of document D4 further suggest that the "coregulators" identified in the document are members of the nuclear receptor superfamily (page 736, left-column, first full-paragraph) (see also document D7, page 9, right-column, line 7 from the bottom to page 10, left-column, first line). This identification is said to be in agreement with the observation of homodimeric and heterodimeric interactions between transcription factors of other known systems, such as in yeast and metazoan

(page 736, left-column, last paragraph) and explicit references are made to the heterodimers of document D1. The teachings of this document are thus fully in line with the ones of document D1 and there is nothing in document D4 that could have prevented the skilled person from following them. Actually, and bearing in mind the explicit assumptions made in this document, the skilled person would have been prompted to further characterize these "coregulators" and then it would have achieved similar results to the ones disclosed in the post-published document D6.

(iv) The teachings of this post-published document D6 are seen as an evident conclusion of the results disclosed in document D4. Both post-published documents D6 and D7 emphasize the relevance of document D1 as first prior art disclosing the presence of heterodimers. Document D1 discloses two heterodimers (human RARα-TRβ and human RARα-rat TRα1), it provides straightforward criteria for selecting further members of this receptor superfamily and it prompts the skilled person to make further heterodimers. In view of this disclosure and the ones found in the prior art (in particular document D4), the board, as argued above, considers that the presence of these heterodimers could hardly be seen as an anomaly and it is in this context that the reference in these post-published documents to the dramatic change of the old "dogma" or the "current model" (steroid/thyroid hormone receptors binding as homodimers) has to be interpreted.

12. In conclusion, the board considers that none of the alleged technical factors would have prevented or hindered the skilled person from using the RXR receptor according to the teachings of document D1 and/or lowered its expectations of success. Starting from D1 in combination with the known prior art concerning the retinoic acid RXR receptor (documents D2 and/or D5), the skilled person would have achieved in an obvious manner and with a reasonable expectation of success subject matter falling under the main request.

In view of the foregoing, the subject matter of independent claim 1 is not seen as inventive and consequently, the main request, which comprises it, is not found to satisfy the requirements of Article 56 EPC.

First auxiliary request (AR-I)
Article 82 EPC

13. According to Article 82 EPC, a European patent application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Rule 30 EPC further reads that the requirement set out in Article 82 EPC shall be fulfilled only when there is technical relationship among those inventions involving one or more of the same or corresponding special technical features, wherein said "special technical features" are those which define a contribution which each of the claimed inventions considered as a whole makes over the prior art.

14. The subject matter of claim 1 of the AR-I is directed to heterodimeric receptors comprising one member selected from isoforms of RXR as a first member and as a second member, one different member of the steroid/thyroid superfamily of receptors selected from

COUP-TF, PPAR, EAR-2 and VDR or another isoform of RXR than the first member. Three technical features are common to all those claimed heterodimeric receptors, namely (i) the fact that they are heterodimers, (ii) the presence of at least one isoform of RXR in all of them and (iii) they all recognize "direct repeat" hormone response elements. However, the presence of general heterodimer receptors is explicitly shown in document D1. Moreover, starting from the disclosure of D1 in combination with the known prior art, the board has decided above that it was obvious for the skilled person to prepare heterodimer receptors having RXR as one of its members and recognizing "direct repeat" hormone response elements. Thus, none of these three technical features can be seen as providing an inventive contribution over said prior art and they are not seen as "special" within the meaning of Rule 30 EPC. The board fails to see in the subject matter of this AR-I any further technical feature which could link the several claimed heterodimeric receptors so as to form a single general inventive concept. Thus, this AR-I is not considered to fulfil the requirements of Article 82 EPC in combination with Rule 30 EPC.

Second auxiliary request (AR-II)

15. This request has been restricted to specific heterodimeric receptors comprising one member selected from isoforms of RXR and COUP-TF.

The presence of both RXR and COUP-TF in all claims is considered to be the "special technical feature" within the meaning of Rule 30 EPC. This technical feature provides the single general inventive concept required by Article 82 EPC.

There is a formal basis for these specific heterodimeric receptors in the application as originally filed (page 9, lines 32 to 36, Examples I and II and combination of claims 5 and 6) and thus, the subject matter of AR-II fulfils the requirements of Article 123(2) EPC.

The claims are clear and fully supported by the description (Examples I and II) and, thus, the conditions of Articles 84 and 83 EPC are considered to be met.

None of the documents on file discloses these specific heterodimeric receptors, which are thus considered to be novel (Article 54 EPC).

The sole remaining issue is whether or not this subject matter fulfils the requirements of Article 56 EPC.

16. The board considers that both the closest prior art (document D1) and the underlying technical problem to be solved (provision of alternative heterodimer receptors of the steroid/thyroid hormone receptor superfamily so as to broaden the range of available regulatory factors of gene transcription) remain the same as those identified above for the main request (points 5 and 6 above).

Starting from document D1 as the closest prior art, the skilled person was faced with two suggestions, namely a conservative and a general one (point 5 above). However, none of these two suggestion would have led the skilled person to the claimed subject matter in an obvious manner. As stated in point 7 above, the skilled person, in agreement with the established case law (cautious attitude), would have followed the first "conservative" suggestion. The board has decided above that the skilled person in question would have then

achieved with a reasonable expectation of success heterodimer receptors having RXR as one of its members. However, the presence of those RXR heterodimers does not rule out that the ability to form heterodimer receptors is exclusively due to an intrinsic property of either RARα and/or TRβ. In order to go one step further and substitute either RARα or TRβ for another member of the steroid/thyroid hormone receptor superfamily, the skilled person would still have to assume that the ability to form heterodimers was not actually limited to RARα and/or TRβ but that it could be generalized to **any** other member of this superfamily. Thus, following both (conservative and general) suggestions, the skilled person would have been confronted with the same general assumption. Whereas based on the teachings and the specific examples shown in document D1, the board has decided above that the skilled person (following the conservative suggestion) would have achieved RXR heterodimers with a reasonable expectation of success, the board concurs with the appellant in that there is no information or hint in the available prior art that could have provided such a reasonable expectation for the above referred general assumption. In fact, the post-published document D6 refers to the RAR/TR receptors as a subgroup which differs functionally from the conventional model of the steroid hormone receptors (page 1409, right-column, third and fourth full-paragraphs) and it clearly stands out as a functionally separate group among the nuclear receptors (page 1416, right-column, third full-paragraph). This is also in agreement with the teachings of the post-published document D7, which refers to the specific properties of TRs and RARs in contrast to the ones of the estrogen receptor and of other steroid hormone receptors (page 9, right-column, last paragraph) as well as to the particular central role of RXR (page 11, Figure 2).

Moreover, the skilled person still was faced with a great number of possible choices among all other members of the steroid/thyroid hormone receptor superfamily. There is nothing in document D1 or in the cited prior art that could have led the skilled person to select in a straightforward manner the specific combination of the AR-II, particularly the selection of the COUP-TF receptor as the second member, among all other possible members of the steroid/thyroid hormone receptor superfamily. Furthermore, the board considers that this selection cannot be seen as an arbitrary one among all other possible choices but it is actually justified by a special technical effect, namely the effect of COUP-TF over the RXR transactivation activity, that is the complete and potent elimination of the RXR-mediated transactivation through the CRBPII promoter with RXR-RE (Example II of the application).

The board further notices that according to the post-published document D7 (Figure 2 and page 13), the inhibitory effects of COUP-TF on RXR-mediated transactivation are achieved by the stronger binding of COUP-TF homodimers to the RXR-response elements and not by the production of RXR-COUP-TF heterodimers. However, the presence of those heterodimers is not clearly excluded and, in the absence of any proof of the contrary, the technical evidence provided by the application (Example 1 and Figure 1) demonstrates that, at least under certain specific conditions, such RXR-COUP-TF heterodimers can be produced. Thus, in the light of the examples shown in the application, it is considered that the claimed subject matter satisfactorily solves the above stated technical problem.

All independent and dependent claims of this AR-II are directed or concerned with these specific heterodimeric RXR-COUP-TF receptors and thus, the subject matter of this AR-II is considered to fulfil the requirements of Article 56 EPC.

Adaptation of the description

17. There are no objections to the amendments to the description which have been effected to bring it into line with the claims of this AR-II.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of:

Claims: 1 to 9 of auxiliary request II filed at oral proceedings on 6 November 2002;

Description: Amended description filed at oral proceedings on 6 November 2002;

Drawings: Figures 1, 2A, 2B and 2C as filed at oral proceedings on 6 November 2002

The Registrar: The Chairman:

A. Wolinski L. Galligani