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D E C I S I O N
of 10 February 2004

Case Number: T 0008/01 - 3.3.8

Application Number: 92903452.8

Publication Number: 0517895

IPC: C12N 15/62

Language of the proceedings: EN

Title of invention:
Chimeric chains for receptor-associated signal transduction pathways

Patentee:
CELL GENESYS, INC., et al

Opponent:
Celltech Therapeutics Ltd

Headword:
Chimeric chain receptors/CELL GENESYS

Relevant legal provisions:
EPC Art. 83, 87, 88, 89, 54, 56, 99(1), 101(1), 114(1)
EPC R. 55(c), 56(1)

Keyword:
"Admissibility of late-filed and fresh grounds for opposition (no)"
"Referral to the Enlarged Board of Appeal (no)"
"Entitlement to priority (yes)"
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
G 0009/91, G 0010/91, G 0007/95, G 0002/98, T 0182/89, T 0019/90

Catchword:

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0008/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 10 February 2004

Appellant: (Opponent)
Celltech Therapeutics Ltd
216 Bath Road
Slough
Berkshire SL1 4EN (GB)

Representative:
Mercer, Christopher Paul
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)

Respondent: (Proprietor of the patent)
CELL GENESYS, INC. et al.
322 Lakeside Drive
Foster City
CA 94404 (US)

Representative:
Wachenfeld, Joachim, Dr.
VOSSIUS & PARTNER
Postfach 86 07 67
D-81634 München (DE)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 3 November 2000 rejecting the opposition filed against European patent No. 0517895 pursuant to Article 102(2) EPC.

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 0 517 895 with the title "Chimeric chains for receptor-associated signal transduction pathways" was granted with 26 claims based on the European patent application No. 92 903 452.8 and claiming priority from US 627643 (14 December 1990).

II. The patent was opposed on the grounds as set forth in Articles 100(a) and (b) EPC that the invention did not involve an inventive step and that it was not sufficiently disclosed. The opposition division found that the ground for opposition under Article 100(b) EPC had not been substantiated in accordance with Rule 55(c) EPC. Even taken account of later submissions by the opponent, the opposition division saw no reason to believe that the invention was insufficiently disclosed in the patent, and it exercised its discretionary power under Article 114(1) EPC, not to consider the ground under Article 100(b) EPC in the opposition proceedings. The other grounds alleged were found not to prejudice the maintenance of the patent. The opposition division rejected the opposition.

III. An appeal was lodged by the opponent (appellant), who requested consideration of the issue of insufficiency under Article 100(b) EPC in the appeal proceedings, or at least, on the basis that there was conflicting case law on the question, referral of two questions to the Enlarged Board of Appeal. Apart from the original objection under Article 56 EPC, an objection under Article 54 EPC (Article 100(a) EPC) was also raised.

IV. The patentee (respondent) filed observations in reply to the statement of grounds of appeal. It asked that the issue of insufficiency under Article 100(b) EPC should not be considered, and saw no necessity to refer any question to the Enlarged Board of Appeal. The respondent did not give its approval to the introduction of the fresh ground for opposition under Article 54 EPC into the appeal proceedings and thus, requested the board to disregard it.

V. The parties were summoned to oral proceedings and, as an annex to these summons, the board sent a communication indicating its preliminary non-binding opinion. In particular, reference was made to the conditions required for admitting the ground for opposition under Article 100(b) EPC into appeal proceedings. Article 54 EPC was considered to be a fresh ground for opposition which could only be considered with the approval of the patentee. The board further indicated its preliminary opinion on the entitlement to the claimed priority and on inventive step, both positively acknowledged.

VI. In reply to the board's communication, the appellant withdrew its request for oral proceedings, announcing at the same time that, in case that these took place, it would not attend them. The appellant indicated that it was content for the appeal to be decided on the papers on file.

VII. The oral proceedings were cancelled.

VIII. Independent claim 1 as granted read as follows:

"1. A chimeric DNA sequence encoding a membrane bound protein, said DNA sequence comprising in reading frame:

a sequence encoding a signal sequence;
a sequence encoding an extracellular binding domain of a surface membrane protein that binds specifically to at least one ligand, wherein said ligand is a protein on the surface of a cell or a viral protein;
a sequence encoding a transmembrane domain; and
a sequence encoding a cytoplasmic domain of a protein capable of transmitting a signal wherein said cytoplasmic domain is the eta or zeta domain of the T cell receptor or the gamma chain of the FcεR1 receptor, wherein said extracellular domain and cytoplasmic domain are not naturally joined together and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric DNA sequence is expressed as a membrane bound protein in a selected host cell under conditions suitable for expression, the binding of a ligand to the extracellular domain leads to transmission of a signal to the cytoplasmic domain, resulting in activation of a signalling pathway in said host cell".

Claims 2 to 8 referred to further embodiments of claim 1. In particular, claims 4, 5 and 6 defined the extracellular domain of claim 1 as being, respectively, the heavy chain of an immunoglobulin (or specific derivatives thereof), CD8 and CD4. Claims 9 and 10 were directed to an expression cassette comprising the DNA sequence of any one of claims 1 to 8, whereas claims 11 to 13 were concerned with a host cell comprising a DNA

sequence of any one of claims 1 to 10. Claims 14 to 19 related to a chimeric protein encoded by said DNA sequence and claims 20 to 23 to a mammalian cell comprising as surface membrane proteins this chimeric protein. Claim 24 was a method for activating these mammalian cells by means of a secondary messenger pathway in vitro. Claim 25 was directed to a retroviral RNA or DNA construct comprising an expression cassette of claims 9 or 10 and claim 26 related to a mammalian cytotoxic- or cytokine-secreting cell according to claims 12 or 20 for pharmaceutical use.

IX. The following documents are referred to in the present decision:

D3: Y. Kuwana et al., Biochem. Biophys. Res. Commun., Vol. 149, pages 960 to 968, 1987;

D6: J-P. Kinet, Cell, Vol. 57, pages 351 to 354, 1989;

D12: J.D. Ashwell and R.D. Klausner, Ann. Rev. Immunol., Vol. 8, pages 139 to 167, 1990;

D14: C. Romeo and B. Seed, Cell, Vol. 64, pages 1037 to 1046, 1991;

D16: B.A. Irving and A. Weiss, Cell, Vol. 64, pages 891 to 901, 1991;

D24: D.J. Capon et al., Nature, Vol. 337, pages 525 to 530, 1989;

D26: D.S. Tyler et al., J. Immunol., Vol. 142, pages 1177 to 1182, 1989.

X. The appellant's arguments in writing, insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of the ground for opposition under Article 100(b) EPC

According to the established case law (*inter alia* T 182/89, OJ EPO 1991, 391), the opposition division had only the power to reject the whole of an opposition as inadmissible but not a particular ground for opposition alone (Article 101 EPC and Rule 56(3) EPC). Since the ground for opposition under Article 100(a) EPC was admissible, the opposition division went beyond its power in holding that the ground for opposition under Article 100(b) EPC was inadmissible. Moreover, in agreement with the Enlarged Board of Appeal decision G 9/91 (OJ EPO 1993, 408) and opinion G 10/91 (OJ EPO 1993, 420), the opposition division could always consider a new ground for opposition, even if it was not mentioned in the notice of opposition, provided that the stipulations set out in Article 114(1) EPC were met. During the opposition proceedings, several arguments were put forward that met the conditions required by Article 114(1) EPC and the patentee had sufficient time to consider them (Article 113(1) EPC). In case that there was a conflict between decision T 182/89, decision G 9/91 and opinion G 10/91, the following questions were requested to be referred to the Enlarged Board of Appeal:

"A. Provided that an admissible notice of opposition, containing at least one adequately substantiated ground

of opposition, has been filed, is an Opposition Division empowered to decide that an inadequately substantiated ground of opposition is inadmissible?

B. Provided that an admissible notice of opposition, containing at least one adequately substantiated ground of opposition, has been filed, and provided that the requirements of Articles 113(1) and 114(2) EPC, have been met, is an Opposition Division empowered to refuse to consider an adequately substantiated ground of opposition introduced into the opposition proceedings after the end of the opposition period?."

Substantive arguments under Article 100(b) EPC

It was argued that since the claimed invention was only exemplified by using (bivalent) monoclonal antibodies, which were known to produce aggregation and cross-linking (capping) of the extracellular domain and, in turn, of the cytoplasmic domain of the claimed chimeric receptors, the patent in suit failed to show that the binding of a specific (monovalent) ligand to the extracellular ligand-binding domain of these chimeric receptors actually led to the transmission of a signal to the cytoplasmic domain. This argument was particularly relevant since the cytoplasmic chains referred to in the patent in suit were known to have a very small extracellular domain with no binding function and to be non-covalently bound to a complex with other cytoplasmic chains. The patent in suit failed to show chimeric constructs containing as cytoplasmic domains the eta chain of the T-cell receptor (TCR) or the gamma chain of the FcεR1 receptor and it was not shown that such constructs were actually

able to activate a signalling pathway in a host cell, even by aggregation of these domains using (bivalent) antibodies as ligands. In this respect, the patent in suit itself showed that the chimeric F1 construct with zeta cytoplasmic and transmembrane domains was not functional. Moreover, there was no disclosure of a DNA construct encoding a chimeric receptor and having a signal sequence. Similarly, there was no disclosure of a chimeric receptor having the extracellular domain derived from an antibody, which was known not to be naturally associated with signalling systems and to differ significantly from the normal extracellular domains of cell surface receptors.

Entitlement to priority (Articles 87 to 89 EPC)

The deficiencies of the patent in suit under Article 83 EPC applied to the priority document, which only disclosed the CD8/zeta construct. Moreover, on reading the priority document, the extracellular domain would be understood to be derived from a naturally occurring protein and there was no suggestion that it could comprise artificial combinations of natural domains. The patent in suit, however, referred to fusion constructs comprising artificial constructs. The meaning of "extracellular domain" was different between the priority document - only natural extracellular domains - and the patent in suit - both natural and artificial extracellular domains. Thus, the claims of the patent were broader than the ones of the priority document and they were not entitled to the claimed priority.

Novelty (Article 54 EPC)

If the board were to hold that the description of the patent in suit was sufficiently disclosed but that the claims were not entitled to the priority date, then at least claims 1 and 14 lacked novelty over document D16, which disclosed a CD8/zeta construct, and document D14, which disclosed a CD4/zeta construct and showed signalling on binding to a natural ligand for CD4 (gp120).

Inventive step (Article 56 EPC)

Document D26, the closest prior art, disclosed the presence of cell receptors for the Fc region of antibodies (FcR) on the surface of NK/K lymphocytes. These receptors were able to bind anti-gp120 antibodies from HIV-1 seropositive patients and NK/K lymphocytes armed with these antibodies targeted and destroyed cells having gp120 molecules on their surface. The binding of antibodies to FcR receptors was said to be a low affinity interaction. Document D26 referred to potential medical applications. However, for these applications, the low binding affinity of FcR receptors to antibodies - further reduced by competition with other circulating antibodies - was an evident technical problem. Thus, the skilled person would have looked for more reliable ways to target these NK/K cells to HIV-infected cells. Document D24 taught that specific binding to HIV-infected cells was achieved using CD4 extracellular domains as specific binding domains for gp120. It was obvious from this document to attach the gp120 binding domain of CD4 directly to the effector part of the FcR receptors of document D26. In order to

activate the NK/K cells, these chimeric receptors would need to associate in the membrane with FcR gamma chains. However, all natural gamma chains constitutively produced by these NK/K cells would be associated with CD16 chains forming the natural FcR receptors. Thus, it would be obvious to the skilled person to attach the gamma cytoplasmic domain directly to the FcR transmembrane domain. In the light of the general prior art concerned with "mix-and-match" of extracellular and cytoplasmic domains with successful signal production and in particular in view of document D3 showing the replacement of a T-cell receptor (TCR) binding domain by an antibody-binding domain which on binding to its antigen triggers a signal by the TCR zeta chain, the skilled person had a reasonable expectation of success. Thus, the claimed subject-matter lacked an inventive step.

Document D3 could also be taken as the closest prior art as done in the decision under appeal. This document explicitly referred to the provision of non-MHC restricted receptors for obtaining ligand-mediated T-cell responses and disclosed chimeric T cell receptors (TCR) with their normal ligand-binding extracellular domain replaced by a ligand-binding domain of an antibody specific for the phosphoryl choline (PC) antigen. T-cells bearing this chimeric TCR were activated on binding to PC. It was evident to the skilled person that these chimeric receptors relied on naturally-produced (endogenous) TCR zeta chain for their activation. However, there was no guarantee that enough endogenous TCR zeta chain would be produced by the transformed T-cells. Thus, the technical problem was to provide a construct which ensured that binding

of antigen to the chimeric receptor caused activation of the cell. In the light of the general prior art concerned with "mix-and-match" of extracellular and cytoplasmic domains with successful signal production, the skilled person would have attached the TCR zeta cytoplasmic domain directly to the chimeric receptor and expected that the binding of the ligand to the resulting chimeric receptor would lead to the activation of the cell. In fact, document D3 went far beyond the patent in suit as it showed that non-MHC restricted receptors could be employed for ligand-mediated T-cell responses, whereas the patent in suit did not use any ligand to obtain the disclosed results and it failed to show any particular advantage over the prior art.

XI. The respondent's arguments in writing, insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of the ground for opposition under Article 100(b) EPC

Both decision T 182/89 and opinion G 10/91 (cf *supra*) required a ground for opposition to be properly supported and substantiated within the 9 months period as defined by Rule 55(c) EPC and Article 99(1) EPC. Rule 55(c) EPC defined the admissibility of the opposition and established at the same time the legal and factual framework within which the substantive examination of the opposition should be conducted. There was neither a contradiction in the established case law nor a need for a referral to the Enlarged Board of Appeal. The arguments supporting the lack of

sufficiency of disclosure were all theoretical assumptions without experimental evidence and thus, they were not substantiated by verifiable facts as required by the established case law (*inter alia* T 19/90, OJ EPO 1990, 476). Thus, the opposition division rightly considered under Article 114(1) EPC that, prima facie, there were no reasons to believe that this ground would prejudice the maintenance of the patent as granted.

Substantive arguments under Article 100(b) EPC

The patent in suit contemplated extracellular domains of chimeric receptors responsive to antibodies and it disclosed the activation of a cell by downstream molecular events (phosphatidylinositol, tyrosine kinase). These events were known to be the effect of induced signal transmission irrespective of whether antibodies or natural ligands were used for stimulation. Moreover, the patent disclosed experiments with cells lacking functional TCR which excluded the activation of T-cell receptors by capping. Whereas the F2 construct was expressed as expected on the cell surface, reasons for the low level of F1 construct were indicated in the patent too, which also provided sufficient teachings to use a signal sequence without undue burden. The eta and gamma cytoplasmic domains had been cloned and were available at the priority date and post-published documents also demonstrated the use of antibody-derived domains as extracellular domains.

Entitlement to priority (Articles 87 to 89 EPC)

The priority document not only disclosed CD8/zeta constructs but it explicitly referred to CD4/zeta constructs too. Both natural and artificial extracellular domains were contemplated in the priority document, which referred to extracellular domains derived from natural immunoglobulins as well as from artificial combinations thereof. The reasons given in support of enablement for the patent in suit applied to the priority document too.

Novelty (Article 54 EPC)

Documents D14 and D16 were published after the priority date and thus, they were not relevant for subject-matter entitled to said priority. An objection under Article 54 EPC was a fresh ground for opposition and, according to G 10/91 (cf *supra*) and G 7/95 (OJ EPO 1996, 626), it could not be raised without patentee's approval. This approval was not given and thus, all submissions concerning lack of novelty were to be disregarded.

Inventive step (Article 56 EPC)

Document D26 disclosed natural killer (NK) lymphocytes having on their surface Fc receptors bound to anti-gp120 antibodies. Even if document D26 referred to possible medical applications, it was not clear whether they could be achieved with antibody armed NK cells since these cells relied on a conglomerate of FcR with the antibody. Moreover, NK cells were not T-cells and thus, the skilled person was not motivated to develop a

system for ligand-mediated T-cell responses. These deficiencies were not overcome by document D24, which disclosed a chimeric serum-bond CD4-IgG with the Ig-domains of the CD4 molecule replacing the V-regions of the gp120 antibody. Macrophages (mononuclear phagocytes) were identified in document D24 as the cells having on their surfaces the FcR with specific affinity for the Fc portion of anti-gp120 antibodies. However, these cells were not T cells and their modification would not lead to a system for ligand-mediated T-cell responses. There was no motivation to attach the extracellular binding domain of CD4 directly to the effector part of the FcR and, since the gamma chain of the FcεR1 receptor had only a very short extracellular domain, it was not expected to trigger a transmembrane signal. The prior art disclosed chimeric receptors obtained from related structurally homologous receptors, whereas the chimeric receptors of the patent in suit were based on the combination of unrelated and structurally entirely different receptors. Moreover, the chimeric receptors of the prior art were known to initiate independently a signalling cascade. However, there was no suggestion in this prior art that any of the eta, zeta or gamma chains alone were capable of initiating a signal or that they were involved in signal transduction. Their actual function was so poorly understood that this precluded any reasonable expectation of success.

Document D3 disclosed T-cells recognising antigens without MHC restriction. These T-cells had on their surface chimeric genes comprising Ig-derived variable regions and T-cell receptor-derived constant regions. Thus, they relied on the combination of two different chimeric molecules (two different V regions) to form a

ligand binding pocket. Starting from document D3 as the closest prior art, the technical problem was to devise novel functional non-MHC restricted receptors for triggering ligand (antigen) mediated responses. The functional chimeric receptors of the patent in suit solved this problem without the disadvantages of the heterodimeric approach. This solution was not derivable from document D3 alone or in combination with any of the prior art on file. Whereas the chimeric receptors of the prior art relied on substitutions among extracellular domains of known receptors with known functions and signal transduction ("mix-and-match approach"), the patent in suit was conceptually different as the eta, zeta or gamma chains comprised a short extracellular domain with no known function. They were neither homologous in function nor similar in structure to the extracellular domains and there was no motivation whatsoever to replace the system of document D3 by another system using those chains. Moreover, since none of the suggested functions for the eta, zeta or gamma chains (chaperone, TcR assembly, regulatory, bridging) included autonomous signal transduction, there was no reasonable expectation of success.

XII. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked in its entirety.

XIII. The respondent (patentee) requested that the appeal be dismissed.

Reasons for the Decision

Admissibility of the opposition

1. Rule 56 EPC, under the heading "Rejection of the notice of opposition as inadmissible", refers to the inadmissibility of an opposition reading in paragraph (1): "*If the Opposition Division notes that the notice of opposition does not comply with the provisions of Article 99, paragraph 1, Rule 1, paragraph 1, and Rule 55, sub-paragraph (c), or does not provide sufficient identification of the patent against which opposition has been filed, it shall reject the notice of opposition as inadmissible unless these deficiencies have been remedied before expiry of the opposition period.*". Thus, it follows from both the heading of Rule 56 EPC and its wording that the concept of "inadmissibility" is only applicable to the Notice of Opposition as a whole. There is no basis in the EPC for the concept of partial admissibility of oppositions.

2. Decision T 182/89 (cf *supra*) refers to a situation wherein "*if a Notice of Opposition **only** alleged insufficiency under Article 100(b) EPC as the **sole** ground of opposition, and only contained such a statement as the only indication of "facts, evidence and arguments" in support of such ground, in the Board's view there would be good grounds for **rejecting such a Notice of Opposition** as inadmissible*" (cf point 2 of the Reasons for the Decision) (emphasis added). In such a situation the Notice of Opposition and the opposition as whole are inadmissible "*even if subsequently proved, (this ground) could provide legal and factual reasons for revoking the patent*" (cf

point 2 of the Reasons). This was not, however, the factual situation underlying decision T 182/89 since, apart from Article 100(b) EPC, the main grounds for opposition were under Article 100(a) EPC and the board remitted the case to the first instance with the order to the opposition division for a decision thereon. No further references is made to the admissibility - or partial admissibility - of the Notice of Opposition or of the opposition.

3. Paragraph 1 of the decision under appeal states: "*The opposition is admissible as it meets the requirements of Articles 99(1) and 100 and of Rules 1(1) and 55 EPC*". There is no reference to the opposition as being only partly admissible, even if one of the grounds for opposition mentioned in the Notice of opposition, namely under Article 100(b) EPC, was considered not to be supported as required by Rule 55(c) EPC (cf point 4 et seq. *infra*). The opposition was admissible as a whole and thus, the decision under appeal was in line with the EPC.

Admissibility of the ground for opposition under Article 100(b) EPC and referral of questions to the Enlarged Board of Appeal

4. Rule 55 EPC in paragraph (c) requires the notice of opposition to contain inter alia "*the grounds on which the opposition is based as well as an indication of the facts, evidence and arguments presented in support of these grounds*", whereas Article 99 paragraph (1) requires that "*Within nine months from the publication of the intention of the grant ... Notice of opposition shall be filed in a written reasoned statement*". According to decision G 9/91 (cf *supra*), Rule 55(c) EPC

has "*the double function of governing ... the admissibility of the opposition and of establishing at the same time the legal and factual framework within which the substantive examination of the opposition in principle shall be conducted*" (cf point 6 of the Reasons for the Decision). It follows from the foregoing that an opposition division shall examine only such grounds for opposition which have been properly submitted and substantiated in accordance with Article 99(1) in conjunction with Rule 55(c) EPC. This is also in line with decision T 182/89 (cf *supra*, point 3.4 of the Reasons).

5. In the present case, the opposition division considered that in the Notice of Opposition filed within the time limit set in Article 99 EPC, the ground for opposition under Article 100(b) EPC was not properly supported, since it was merely stated that the patent in suit failed to exemplify some embodiments but no evidence was provided that these embodiments could only be achieved with undue burden or else that they failed to function as taught in the patent in suit. The board sees no reasons to disagree with this assessment.

6. As regards the obligation of an opposition division to consider all grounds for opposition, the Enlarged Board of Appeal in decision G 9/91 (cf *supra*, point 15 of the Reasons) confirmed the findings of T 182/89 (cf *supra*) indicating that Article 114(1) EPC was **not** a legal basis for an **obligatory** review of grounds of opposition not properly covered by the statement pursuant to Rule 55(c) EPC. The same decision (cf point 16 of the Reasons) also stated that **exceptionally** the opposition division may, in application of Article 114(1) EPC,

consider other grounds for opposition not properly covered which, *prima facie*, in whole or in part would seem to prejudice the maintenance of the European patent. As the criteria laid down in decision G 9/91 (cf *supra*) have already clarified the point of law of the power to examine and there is no apparent contradiction in the case law established since then, the board does not see any need to refer any of the questions proposed by the appellant to the Enlarged Board of Appeal (cf Section X *supra*).

7. In fact, after expiry of the time limit set in Article 99(1) EPC, the opposition division, in line with the criteria set out in decision G 9/91 (cf *supra*), used its discretionary power under Article 114(1) EPC and gave a *prima facie* consideration to the later submissions by the opponent concerning Article 100(b) EPC (cf point 3.4 of the decision under appeal). However, these submissions were not considered, prima facie, to prejudice the maintenance of the patent as granted and the ground for opposition under Article 100(b) EPC was disregarded. It remains to be assessed whether the opposition division, in the light of these late filed submissions, exercised its discretion wrongly, ie in a manner that no reasonable opposition division would have exercised it.

Substantive arguments under Article 100(b) EPC

8. The objections raised under Article 100(b) EPC in these late submissions were essentially of two different types. Firstly, it was objected that several embodiments were not exemplified in the patent in suit, such as eta or gamma chains as cytoplasmic domains, an

antibody-derived extracellular domain, signal sequences. Secondly, it was objected that since the patent in suit gave no exemples of monovalent ligands but only of bivalent antibodies with clustering (capping) of extracellular and cytoplasmic domains, it failed to demonstrate that the chimeric receptors functioned as required in the granted claims.

9. The substitution of the exemplified zeta chain of the T-cell receptor by one of the other non-exemplified two chains does not require any special skill or place an undue burden on the skilled person since all the technical information - sequence, source, methods, etc. - was available in the prior art as shown by the literature cited in the description of the patent in suit and that on file. A similar conclusion is reached for the substitution of the exemplified extracellular domains (CD8, CD4) by an antibody-derived domain or for the use of a signal sequence in the construction of chimeric DNA sequences.

10. The description of the patent in suit explicitly refers to antibodies as ligands of the disclosed chimeric receptors (cf page 3, lines 48 to 49 of the patent as published). The allegation that the chimeric receptors do not function as required in the granted claims was not supported by any experimental evidence or piece of prior art. On the contrary, there is evidence on file supporting that the suggested function was actually achieved. The patent in suit shows activation of intracellular signalling events and significant results in cells lacking surface expression of T-cell receptors. Even if for a particular construct (F1) low levels of cell surface expression were detected, reasons thereof

are explicitly given in the patent in suit (cf page 11, lines 49 to 55). Moreover, post-published document D14 (to be taken as technical expert evidence) shows that the chimeric receptors disclosed in the patent in suit work - on binding to monovalent ligands - as suggested therein (transmission of a signal and activation of a signalling pathway).

11. In view of the above considerations, the board considers that the opposition division exercised in a reasonable manner its discretion as to whether it should raise the ground of opposition under Article 100(b) EPC itself, said ground not having been properly covered by the statement pursuant to Rule 55(c) EPC and having been substantiated only by later submissions. Thus, the ground of opposition under Article 100(b) EPC, which at this stage could be introduced **only** with agreement of the respondent (cf G 7/95 *supra*), said agreement being denied here, is disregarded.

Entitlement to priority (Articles 87 to 89 EPC)

12. According to opinion G 2/98 (OJ EPO 2001, 413), priority of the same invention is to be acknowledged only if the skilled person derives the **same subject-matter** of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

13. Appellant's submissions are mainly based on two different lines of argumentation, namely (i) a lack of enablement of the priority document because several embodiments were not exemplified and the chimeric

receptors were not shown to have the required function or effect, and (ii) a difference in the meaning of the term "extracellular domain" between the priority document - narrow and specific for naturally-occurring extracellular domains - and the patent in suit - broad and comprising both naturally-occurring and artificial extracellular domains.

14. The priority document exemplifies only the CD8/zeta chimeric receptor. However, all the other chimeric receptors referred to in the patent in suit are also explicitly mentioned in this priority document (cf *inter alia* page 4, lines 19 to 27 and claims 1 and 17 of the priority document). The substitution of the zeta domain of the T-cell receptor by the eta domain of the same receptor or the gamma chain of the FcεR1 receptor as cytoplasmic domains of the claimed chimeric receptors does not require any special skills or place undue burden on the skilled person since all the technical information - sequence, source, methods, etc. - was available in the prior art as shown by the literature cited in the priority document (cf pages 2 and 3). A similar conclusion is also achieved for other embodiments not exemplified in the priority document, in particular an antibody-derived extracellular domain (cf point 16 *infra*) and the use of signal sequences in the construction of a DNA sequence encoding the chimeric receptors. Thus, the fact that not all specific embodiments were exemplified in the priority document is irrelevant since all of them could be achieved on the basis of the information given without requiring any inventive skill and without an undue burden.

15. The priority document discloses the activation of intracellular signalling events (phosphatidylinositol, tyrosine kinase pathway) on binding of a ligand to the exemplified the CD8/zeta chimeric receptor and it further refers to significant results in cells lacking surface expression of T-cell receptors (cf pages 17 to 25). Although the priority document exemplifies only the use of bivalent antibodies as ligands, which are known to cluster (capping) the extracellular and the cytoplasmic domains, there is evidence on file showing that this effect is also achieved by other ligands too. In particular, post-published document D14 (to be taken as technical expert evidence) discloses chimeric receptors comprising a CD4 extracellular domain and, as cytoplasmic domains, either zeta or eta chains of the T-cell receptor or the gamma chain of the FcγRIII, which is said to be a component of FcεRI too (cf page 1037, right-hand column, last full paragraph). These chimeric receptors are shown to trigger cytolytic effector programs on binding to their ligands (gp120/gp41). Thus, in the light of the evidence on file, there are no reasons to doubt that the chimeric receptors disclosed in the priority document function as suggested therein.

16. Several claims of the priority document refer to the extracellular domain of the claimed chimeric receptors as being "*the heavy chain of an Ig, by itself or in conjunction with a light chain*" (cf *inter alia* claim 3 of the priority document). There is no limitation or any special requirement attached to this conjunction and, in the light of the references found on page 6 and on page 7, lines 14 to 32, concerned with the extracellular domain, in particular on page 7, lines 19

to 23, which reads "... *The deletion or insertion of amino acids will usually be as a result of the needs of the construction, providing for convenient restriction sites, ease of manipulation, improvement in levels of expression, or the like ...*", the board fails to see - either explicitly or implicitly - any limitation or restriction to naturally-occurring extracellular domains. On the contrary, the broad meaning of the term extracellular domain - including artificial, modified and variants thereof - as understood to be present in the patent in suit, is already found directly and unambiguously in the priority document too.

17. It follows from the foregoing that the priority document is enabling (cf points 14 and 15 *supra*) and that the meaning of the term extracellular domain is the same in both the priority document and the patent in suit (cf point 16 *supra*). Thus, the patent in suit is entitled to the claimed priority.

Novelty (Article 54 EPC)

18. In the Notice of Opposition only a lack of inventive step (Article 56 EPC) was indicated and argued as a ground of opposition under Article 100(a) EPC. No objection was raised against the novelty of the subject-matter claimed in the patent in suit (Article 54 EPC). This ground for opposition was also not subsequently introduced in the opposition proceedings. It is a fresh ground for opposition raised for the first time in the statement of Grounds for Appeal. According to decision G 7/95 (cf *supra*) in a case where a patent has been opposed under Article 100(a) EPC on the ground that the claims lack

an inventive step in view of documents cited in the Notice of opposition, the ground of lack of novelty based upon Articles 52(1), 54 EPC is a fresh ground for opposition and accordingly may not be introduced into the appeal proceedings without the agreement of the patentee. In the present case, the patentee has failed to give its consent and thus, the fresh ground for opposition may not be introduced into appeal proceedings. However, as indicated in the same decision the allegation that the claims lack novelty in view of the closest prior art document may be considered in the context of deciding upon the ground of lack of inventive step.

19. In the case at issue the objection raised under Article 54 EPC relied on documents D14 and D16, which were both published on March 1991 and thus, well after the claimed priority (14 December 1990). In view of the finding on priority which has been acknowledged (cf points 13 to 17 *supra*), none of these documents constitutes relevant prior art under Article 54(2) EPC. Thus, no novelty objection applies.

Inventive step (Article 56 EPC)

20. Two documents have been referred to as closest prior art depending on whether the cytoplasmic domain of the claimed chimeric receptor belongs to T-cell receptors (eta and zeta chains) or else to FcεR1 receptors (gamma chain), namely document D3 and document D26, respectively.

Embodiments in relation to the eta or zeta chain of the T-cell receptor:

21. Starting from the observation that α and β chains of the T-cell receptor (TCR) are "*rather similar to those of Ig*", document D3 studies whether the difference in antigen recognition between MHC-restricted T-cells (which do not recognize antigen alone but only in association with MHC molecules) and MHC-unrestricted B-cells (which do not require MHC to recognize the antigen) derives from structural differences in their extracellular domains (variable (V) regions) (cf document D3, paragraphs bridging pages 960 to 961 and pages 965 to 967). Document D3 discloses genes encoding chimeric receptors comprising immunoglobulin-derived variable (V) regions as extracellular domains and T-cell receptor (TCR)-derived constant regions as cytoplasmic domains, these V regions being specific for the antigen phosphorylcholine (PC). Two pairs of chimeric genes (V_L-C_β and V_H-C_α genes and V_L-C_α and V_H-C_β genes) are used to obtain transformed cells expressing both chimeric receptor molecules. The chimeric receptors expressed on the transformant cells are able to react with the specific PC antigen and to trigger T-cell activation (increase in the cytosolic calcium). Further studies are said to be required in order to assess whether helper and cytolytic functions also occur. If this is the case, document D3 concludes that "*... in future, it might become possible for T cells recognizing any antigen without MHC-restriction to be produced ...*" (cf page 967, lines 1 to 7).

22. Starting from this prior art, the objective technical problem underlying the patent in suit is the provision of alternative MHC-unrestricted chimeric T-cell receptors. The solution proposed is represented by

chimeric receptors wherein the cytoplasmic domain is the eta or zeta chain of the T-cell receptor, and methods and means for producing them and uses thereof. The board is satisfied that the chimeric receptors disclosed in the patent in suit solve this technical problem.

23. In the light of document D3, which explicitly emphasizes the similarity between the α and β chains of the TCR and Ig (cf point 21 *supra*), the skilled person faced with the technical problem stated above, would have first tried to look for Ig-derived chains with alternative antigen-specificity or, if at all, other chains with significant similarity to the ones used in document D3. In fact, document D3 itself refers to other studies wherein reverse chimeric genes are disclosed, in particular the combination of TCR-derived extracellular domains and Ig-derived cytoplasmic domains. Apart from these studies, document D3 does not, however, hint at any other extracellular or cytoplasmic domain. In view of the fact that both eta and zeta cytoplasmic chains were known from the prior art to be - structurally and functionally - very different from Ig-derived chains or from the α and β chains of the TCR (cf *inter alia* document D12), the substitution of these latter chains for the eta or zeta chains would not have been evident to the person skilled in the art. As regards the appellant's argument that the low levels of available endogenous eta and zeta chains of the TCR on which the chimeric receptors of document D3 allegedly rely for activation would have prompted the skilled person to attach such chains to the extracellular domains, the board fails to see any such indication - either explicit or implicit - in document D3. Nor is

this view supported by any prior art on file. Thus, starting from document D3, the claimed subject-matter is **not obvious**.

Embodiments in relation to the γ chain of the FcεR1 receptor:

24. Document D26, relied upon by the appellant as closest prior art, discloses a non-MHC restricted g120 specific cell-mediated cytotoxicity (CMC) in fresh circulating peripheral blood mononuclear cells (PBMC) from HIV-1 seropositive individuals. This CMC is shown to be mediated by the presence of cytophilic anti-gp120 antibodies bound directly to the surface of $CD16^+$ (FcR) natural killer (NK/K) lymphocyte cells via their Fc receptors (FcR). This CMC corresponds to a form of direct antibody-dependent cellular cytotoxicity (ADCC) mediated by FcR bearing effector NK/K cells armed with cytophilic anti-gp120 antibodies, ie antibody armed effector cells. The therapeutic importance of armed NK/K cells with their ability to mediate non-MHC restricted killing to destroy foreign virally infected cells is explicitly mentioned in the document (cf page 1181, right-hand column, last paragraph). However, document D26 also refers to the low binding affinity between the cytophilic antibodies and the FcR on NK/K cells as well as the high binding affinity of FcR with anti-CD16 antibodies, which could prevent these NK/K cells from serving as receptors for gp120 (cf page 1181, left-hand column, first full paragraph).

25. It is observed that, in comparison to the patent in suit, there is no disclosure of a chimeric receptor in document D26, not even a suggestion or a reference to its possible relevance. Moreover, document D26 is

completely silent on the FcεR1 receptor and, particularly, on the γ chain of this receptor. Thus, in the light of these important technical differences, the board considers that document D26 is not an appropriate starting point for a discussion of inventive step.

26. The appellant, starting from document D26, has formulated as a technical problem the provision of an improved binding affinity between the gp120 and the NK/K cells so as to increase the CMC effect of these cells. In its view, since the high affinity of the cell surface glycoprotein CD4 for gp120 was known from document D24, an obvious technical solution to the above formulated technical problem would have been the production of a chimeric receptor comprising the effector part of the FCR receptor (cytoplasmic domain) with the extracellular domain of CD4. However, even if this was accepted, there still remains the substitution of the effector part of the FcR receptor for the γ chain of the FcεR1 receptor. There is no - either explicit or implicit - indication in documents D26 or D24 of the alleged critical importance of this chain, let alone of a possible deficiency of its (endogenous) amount in NK/K cells, nor is the importance of this directly derivable from any other prior art document on file. Moreover, in the light of the important structural and functional differences between the FcγR (cf document D26, page 1181, left-hand column, last paragraph) and the FcεR receptors as well as their presence in different cell populations (cf document D6, page 352, right-hand column, second full-paragraph and Figure) and of the fact that neither the function of the γ chain of FcεR in signal transduction nor its structural association with other components of the FcR

receptors were clearly known (cf document D6, paragraph bridging pages 353 to 354), the proposed substitution was **not evident** to the skilled person from said document taken alone or in combination with any other of the documents on file.

Conclusion

27. In view of the above, the board considers that the claimed subject-matter fulfils the requirements of Article 56 EPC. Thus, the patent in suit satisfies the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani