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Datasheet for the decision of 18 October 2022

Case Number: T 0498/18 - 3.3.04

Application Number: 10774475.7

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Language of the proceedings: EN

Title of invention:
Compositions and methods for treating hematologic cancers targeting the CD47-SIRPα interaction

Patent Proprietor:
University Health Network
The Hospital For Sick Children

Opponents:
Leeming, John Gerard
James Poole Limited

Headword:
soluble SIRP-alpha/UNIVERSITY HEALTH NETWORK

Relevant legal provisions:
EPC Art. 54, 56, 111(1)

Keyword:
Novelty - (yes)
Inventive step - (yes)
Remittal to the department of first instance (yes)

Decisions cited:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0498/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 18 October 2022

Appellant: (Patent Proprietor 1)	University Health Network 190 Elizabeth Street R. Frazer Elliott Building - Room 1S-417 Toronto, Ontario M5G 2C4 (CA)
Appellant: (Patent Proprietor 2)	The Hospital For Sick Children 555 University Avenue Toronto, Ontario M5G 1X8 (CA)
Representative:	Dempster, Robert Charles Script IP Limited Turnpike House 18 Bridge Street Frome Somerset BA11 1BB (GB)
Respondent I: (Opponent 1)	Leeming, John Gerard J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
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Respondent II: (Opponent 2)	James Poole Limited One Southampton Row London WC1B 5HA (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 2 January 2018 revoking European patent No. 2429574 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman M. Pregetter
Members: O. Lechner
P. de Heij

Summary of Facts and Submissions

I. The appeal of the patent proprietors (appellants) lies from the decision of the opposition division to revoke European patent No. 2 429 574 (the patent).

II. The patent is based on European patent application No. 10 774 475.7, which had been filed as an international application and published as WO 2010/130053 (application as filed).

III. The patent was opposed on the grounds set out in Article 100(a) (for alleged lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC)), 100(b) and 100(c) EPC.

IV. In the decision under appeal, the opposition division decided that:

- the main request contained subject-matter which extended beyond the content of the application as filed within the meaning of Article 100(c) EPC
- auxiliary requests 1 to 13 contained subject-matter which extended beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC
- claim 1 of auxiliary requests 14 to 23 lacked an inventive step (Article 56 EPC)

V. With the statement of grounds of appeal, the appellants filed sets of claims of a main request (corresponding to auxiliary request 14 in the decision under appeal) and nine auxiliary requests.

VI. Opponents 1 and 2 (respondent I and respondent II) replied to the statement of grounds of appeal.

VII. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA 2020.

In this communication, the board indicated that:

- the subject-matter of claim 1 of the main request and auxiliary requests 1 to 9 appears to be novel over the disclosure in documents D4 and D49
- starting from document D16 as the closest prior art for assessing inventive step, the objective technical problem could be seen as the provision of an alternative compound capable of blocking the CD47-Sirpα interaction for use in a method for treating CD47+ haematological cancer cells in a patient

VIII. Oral proceedings before the board took place on 18 October 2022 in the form of a videoconference. At the end of the oral proceedings, after the final requests had been established, the Chairwoman announced the board's decision.

IX. The following documents are cited in the present decision:

D1: Y. Liu *et al.*, J. Mol. Biol., 365(3), 2007, 680-93

D4: WO 99/40940 A1

D6: WO 2009/046541 Al

D7: N. Barclay *et al.*, Nature Reviews, 6, 2006, 457-64

D8: K. Takenaka *et al.*, Nature Immunology, 8(12), 2007, 1313-23

D12: K. Ide *et al.*, PNAS, 104(12), 2007, 5062-6

D13: T. Matozaki *et al.*, Trends in Cell Biology, 19(2), 2009, 72-80

D14: R. Majeti *et al.*, Cell, 138(2), 2009, 286-99

D16: R. Majeti *et al.*, Blood, 112(11), 2008, 766

D17: R. Reid (Editor), Peptide and Protein Drug Analysis, 2000, 616

D18: M. Seiffert *et al.*, Blood, 97(9), 2001, 2741-9

D19: S. Jaiswal *et al.*, Trends Immunol., 31(6), 2010, 212-9

D48: H. Umemori *et al.*, J. Biol. Chem., 283(49), 2008, 34053-61

D49: WO 2009/131453 A1

D50: WO 2004/096133 A2

D51: X.W. Zhao *et al.*, Europ. J. Clin. Invest., 39(Suppl. 1), 2009, Abstract 636

D52: E.F. Vernon-Wilson *et al.*, Eur. J. Immunol., 30, 2000, 2130-7

D53: J. Holash *et al.*, PNAS, 99(17), 2002, 11393-8

D54: A.N. Economides *et al.*, Nature Medicine, 9(1), 2003, 47-52

D55: WO 2014/094122 A1

X. Independent claims 1 and 14 of the main request read:

"1. A compound for use in a method for treating hematological cancer cells that are CD47+ in a patient, the compound comprising a polypeptide capable of binding to the extracellular domain of human CD47 to interrupt signaling between human Sirpα and human CD47, wherein the polypeptide comprises soluble human Sirpα, or a CD47-binding fragment thereof."

"14. A pharmaceutical composition for use in treating a hematological cancer with cancer cells that are CD47+, comprising an effective amount of a compound as defined in any one of claims 1-8 and l3 and a pharmaceutically acceptable carrier."

XI. The appellants' arguments relevant to the decision are summarised as follows.

Main request

(a) Novelty - Article 54 EPC
There was nothing to add to the opposition division's decision and the board's finding in the communication under Article 15(1) RPBA that the claimed subject-matter was novel.

(b) Inventive step - Article 56 EPC

Closest prior art

Document D16 represented the closest prior art and disclosed that cluster of differentiation 47 (CD47) was increased on human acute myeloid leukaemia (AML)

stem cells (LSC) compared to normal haematopoietic stem cells (HSC). Increased CD47 was associated with worse event-free and overall survival. Document D16 also suggested that mouse anti-human CD47 monoclonal antibodies (mAb) enabled phagocytosis of AML LSC by both mouse and human macrophages *in vitro*, and that anti-CD47 mAb eliminated leukaemia cells in NOD/Shi-*scid*/IL-2Rγ^{null} (NOG) mice *in vivo, i.e.* that anti-CD47 antibodies could potentially be used for treating leukaemia.

The anti-CD47 antibody used in document D16 was not further characterised.

Difference and problem to be solved

The subject-matter of claim 1 differed from the teaching in document D16 in that soluble human signal regulatory protein α (SIRPα) or a CD47-binding fragment thereof was used to treat haematological cancer.

The problem to be solved was the provision of an alternative compound for use in treating haematological cancer.

Obviousness

Document D16 did not provide a teaching going beyond the use of anti-CD47 antibodies. Starting from the teaching of document D16, at least three assumptions had to be made to arrive at soluble SIRPα.

- First, it had to be surmised, in the absence of any disclosure in this direction, that the anti-CD47 antibody of document D16 was working by disrupting the receptor interactions.

- Second, it had to be assumed that any other agent disrupting the interaction had to be expected to have a similar effect.

- Third, it had to be considered certain that specifically soluble SIRPα would work the same way as the anti-CD47 mAb in treating haematological cancer.

However, none of these three assumptions was fulfilled.

Document D16 failed to provide any information on how the anti-CD47 antibody worked. Thus, it was not known whether it was antagonistic or agonistic, and it was not shown that its sole effect and the effective mechanism was the disruption of the CD47-SIRPα interaction. However, an understanding of the action mechanism of the antibody would have been necessary to extrapolate the teaching to alternative agents.
It was not clear to the skilled person whether the CD47-SIRPα interaction suppressed or stimulated macrophage activity. Several prior-art documents, such as D1, D4, D6, D7, D13 and D18, taught that the interaction between these two receptors was crucial in promoting immune responses, especially the responses of T cells and macrophages. By disrupting this interaction, a suppression of the immune response had to be expected. This was in complete contrast to what was necessary in the treatment of cancer.

As shown in Figure 1 of document D7, the interaction of CD47 and SIRPα was complex; both receptors were capable of binding to different ligands and signalling in different directions.

This lack of knowledge was also reflected by the cautious language in document D16: "*We hypotesize [...]*", "*One prediction from this hypothesis [...]*" and "*A second prediction from our hypothesis[...]*".

Also, other documents such as D1, D6, D13, D14, D18, D48 and D51 showed that the CD47-SIRPα interaction had multiple effects on the immune system such as phagocytosis and that it was not clear whether soluble SIRPα would have the same effect as an anti-CD47 antibody.

Thus, it was not known from any of the prior-art documents whether soluble SIRPα had the same effect as an anti-CD47 antibody or a completely different one.

XII. The respondents' arguments relevant to the decision are summarised as follows.

Main request

(a) Novelty - Article 54 EPC

Lack of novelty over document D4 - Article 54(2) EPC

The fragments of SIRPα disclosed in document D4 encompassed soluble SIRPα. It was implicit from the disclosure in this document that it referred to human SIRPα since the ligands were designed for use in pharmaceutical compositions for treating human diseases. No selection from lists was required to arrive at the subject-matter of claim 1. The treatment of chronic lymphocytic leukaemia (CLL) using ligands of CD47 was specified in a single sentence on page 11, lines 17 to 18 of document D4, and SIRPα and fragments thereof were disclosed as a preferred ligand of CD47.

Therefore, the teaching of document D4 anticipated the claimed subject-matter.

Lack of novelty over document D49 - Article 54(3) EPC

Document D49 was citable for novelty under Article 54(3) EPC and provided a direct and unambiguous disclosure of agents that block the interaction between CD47 and SIRPα for treating haematological cancers such as CLL, with a preferred agent being a soluble N-terminal fragment of SIRPα. Agents, such as peptides, that could interfere with the interaction between SIRPα and CD47 were described in detail on page 7 of document D49. Page 7, lines 25 to 27 of D49 specified that "*[p]referably, the peptides are derived from the N-terminal V-type immunoglobulin domains in SIRPα or CD47 which are responsible for SIRPα-CD47 interaction*". Thus, soluble SIRPα derived peptides were highlighted as a preferred agent for inhibiting the CD47-SIRPα interaction.

Page 10 of document D49 specified that CD47-SIRPα interaction inhibiting agents were useful in treating "*a disease or disorder that would benefit from enhanced phagocytosis by macrophages*". Examples of diseases that would benefit from enhanced phagocytosis were specified on page 10, lines 9 to 10: "*non-Hodgkin's lymphoma, breast cancer, chronic lymphocytic leukaemia or colorectal cancer*". Document D49 related to agents for treating human diseases, and accordingly it was evident that the agents referred to in D49 would be derived from human proteins.

Thus, the teaching of document D49 anticipated the claimed subject-matter.

(b) Inventive step - Article 56 EPC

Closest prior art

Document D16 (filed by opponent II as D9 in the proceedings before the opposition division) represented the closest prior art.

Document D16 reported increased expression of CD47 on human AML LSC and that interrupting the CD47-SIRPα interaction with an anti-CD47 antibody enabled phagocytosis of the AML LSC cells *in vitro* and *in vivo* and the elimination of these cells.

Difference and problem to be solved

The difference between the claimed subject-matter and D16 was the use of soluble SIRPα to disrupt the CD47-SIRPα interaction to treat leukaemia instead of an anti-CD47 antibody.

The problem to be solved was the provision of an alternative compound to the anti-CD47 antibodies described in document D16 for use in a method of treating haematological cancer cells that are CD47+ in a patient (opponent 1) or providing an alternative CD47-binding agent capable of inhibiting the interaction of CD47 with SIRPα (opponent 2).

Obviousness

Document D16 made clear that the anti-CD47 antibody tested had to block the CD47-SIRPα interaction. The authors of this document knew from the prior art that increased CD47 expression was detrimental for leukaemic

cells and that it worsened the clinical outcome. Document D16 explicitly taught that disruption of the CD47-SIRPα interaction enabled the phagocytosis of leukaemic cells *in vitro*. Moreover, coating of AML LSC with anti-CD47 antibody completely eliminated *in vivo* engraftment upon xenotransplantation into NOG mice.

It was apparent that the anti-CD47 antibody of document D16 worked via the disruption of the CD47-SIRPα interaction with the aim of activating phagocytosis, an effect already known in the art as evidenced, e.g. by documents D7, D8 and D12.
No document cited by the appellants called into question the mechanism disclosed in document D16.

Given the reported *in vivo* anti-cancer effect of interfering with the CD47-SIRPα interaction reported in document D16, the appellants' argument that document D4 demonstrated an immunosuppressive effect for soluble SIRPα was unfounded.

Soluble SIRPα, or a CD47 binding fragment of it, was an obvious alternative to the anti-CD47 antibodies suggested in D16.

Numerous documents demonstrated that soluble receptors, typically receptor-Fc fusion proteins, were routinely used at the priority date to block receptor signalling interactions, as evidenced for example in document D17, D18, D53 and D54. Many prior-art documents such as D1, D6, D11, D12, D18, D49, D50 and D52 disclosed soluble SIRPα polypeptides and identified soluble CD47-binding fragments of SIRPα.

Document D6 and D18 presented soluble SIRPα as an alternative to an anti-CD47 antibody for inhibiting CD47-SIRPα interaction.

Document D6 related primarily to modulating the CD47-SIRPα interaction in the context of affecting HSC engraftment. The data in document D6 did not address the role of this interaction in the context of haematological cancer. However, the results of document D6 (see e.g. Examples 8 and 14) showing that enhancement of the CD47-SIRPα interaction led to reduced phagocytosis and thus improved engraftment were consistent with the teaching of D16.
The appellants had relied heavily on claim 19 of document D6. This claim set out the desired effect consistent from the examples, namely that an increased HSC engraftment resulted from the suppression of macrophages. Although the appellants used this claim to argue that document D6 taught that soluble SIRPα would suppress macrophages, this was inconsistent with the teaching in the examples of document D6, which did not use soluble SIRPα in this context. In fact, the examples of document D6 used expression of SIRPα within macrophages to induce the suppressive effect.

Document D18 also taught to use soluble SIRPα or anti-CD47 antibodies for interfering with the interaction of these two receptors (see page 2747, left-hand column, second full paragraph ff.), i.e. exactly what document D16 required. Given the clear *in vivo* anti-cancer effect of anti-CD47 antibodies outlined in document D16, it was not relevant that a cytotoxic T-lymphocyte (CTL) inhibitory effect was reported in document D18 for soluble SIRPα and anti-CD47 antibodies in the system tested.

In fact, the appellants themselves were able to arrive at soluble SIRPα as a suitable agent for inhibiting the CD47-SIRPα interaction for treating leukaemia without any data demonstrating this effect. The priority document comprised no experimental data on the use of soluble SIRPα. Nevertheless, the inventors concluded that "*[i]nterruption of CD47-SIRPα signaling through targeting of either CD47 or SIRPα is a potential therapeutic approach for eradication of hematological cancers cells such as leukemic stem cells, preferably AML-LSC*", (see application as filed, page 25, line 4 to 6) after having referred to the data in document D16 (see application as filed page 24, line 24). The conclusions drawn by the inventors in the priority document were at odds with the apparently complex CD47-signalling situation alleged by the appellants.

XIII. Requests of the parties

The appellants requested that:

- the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims according to the main request or one of auxiliary requests 1 to 9
- the case be remitted to the opposition division if the opponent's objections under Article 83 EPC needed to be taken into account
- the proceedings be stayed in view of pending referral G 2/21 if the post-published evidence in documents D23, D24 or D55 was considered crucial

The respondents requested that:

- the appeal be dismissed and that the decision to revoke the patent be maintained
- the case be remitted to the opposition division for discussion of sufficiency of disclosure

- auxiliary request 9 not be admitted into the proceedings

Reasons for the Decision

Main request

1. Novelty (Article 54 EPC)

1.1 Document D4 - Article 54(2) EPC

1.1.1 Document D4 discloses the use of ligands of CD47, preferably selected from the group consisting of anti-CD47 antibodies, thrombospondin, Tp47 (a thrombospondin-derived peptide binding to CD47), SIRPα and fragments thereof, and/or binding agents of these ligands in the treatment or prophylaxis of various inflammatory autoimmune and allergic diseases as well as in the treatment of graft rejection and CLL (see page 3, paragraphs 2 and 5; claims 5 and 11).

As pointed out by respondent I, page 11, line 17 to 18 of document D4 mentions CLL together with CD47 ligands in a separate sentence. However, this sentence needs to be read in the context of the whole paragraph (starting at line 9), which states that "*[t]he present inventor is thus of the opinion that ligands of CD47 in general as well as agents binding to the ligands of CD47 could be useful in the treatment or prophylaxis of various inflammatory, autoimmune and allergic diseases as well as in treatment of tumor metastasis, cachexia and graft rejection*". What follows is a list of specific inflammatory, autoimmune and allergic conditions that can be treated, and the final sentence that "*[c]hronic lymphocytic leukemia (CLL) could also be treated using the ligands of CD47 of the invention*".

CLL is not singled out or labelled as a preferred disease to be treated but is mentioned as one of the many conditions that can be treated with CD47 ligands.

In addition, while explicitly disclosing soluble CD47-Fc (see e.g. abstract; page 4, first full paragraph; Figure 17), there is no direct and unambiguous disclosure that the SIRPα fragments may be soluble human SIRPα polypeptides.
Document D4, thus, does not anticipate the subject-matter of claim 1 within the meaning of Article 54(2) EPC.

1.2 Document D49 - Article 54(3) EPC

1.2.1 Document D49 discloses the use of a CD47/SIRPα inhibitory agent to enhance a host's immune effector cells (see page 4, paragraph 1). Document D49 fails to disclose the combination of the features of claim 1 of the current main request. To arrive at the claimed subject-matter, a selection from multiple lists of alternatives is required.

According to document D49, the "agent" or "antagonist" of D49 has to be selected from among small molecules, an antibody or a proteinaceous substance. The proteinaceous substance could be either a peptide, an antibody or an antibody fragment (see page 7, lines 22 to 23). Suitable peptides could be derived from SIRPα, CD47 or another polypeptide involved in the functional CD47-SIRPα interaction (page 7, lines 23 to 25).
Page 7, line 28 ff states that "*[p]referred agents are antibodies of antibody fragments*", and the examples also use anti-SIRPα antibodies (see Examples 1 to 4).
Thus, a SIRPα derivative is not highlighted as a

preferred embodiment, and a first selection from a list of alternatives is required.

CLL has to be selected from a second list of various alternative diseases, ranging from different cancers including CLL (see page 10, first full paragraph; claim 6) to viral infections (see page 10, paragraph 2; claim 7).

1.2.2 Thus, the claimed combination of soluble SIRPα as the CD47/SIRPα inhibitory agent and CLL as the disease to be treated is not directly and unambiguously disclosed in document D49, and the claimed subject-matter is novel over the teaching in this document.

2. Inventive step

The invention relates to interrupting the CD47-SIRPα interaction to treat haematological CD47+ cancer, particularly human AML using soluble human SIRPα or a CD47-binding fragment thereof.

Closest prior art

2.1 The board agrees with the parties that document D16 represents a suitable starting point for assessing inventive step.

Document D16 reports an increased expression of CD47 on human AML LSC compared to normal HSC. Differential CD47 expression can be utilised to prospectively separate normal ($CD47^{low}$) from leukaemic ($CD47^{high}$) progenitors from the same patient sample. The authors hypothesise that increased CD47 expression on human AML would contribute to pathogenesis by inhibiting phagocytosis of leukaemia cells through the interaction of CD47 with

SIRPα. Increased CD47 expression was found to be associated with worse event-free and overall survival. Disruption of the CD47-SIRPα interaction with an anti-CD47 mAb enabled phagocytosis of AML LSC by both mouse and human macrophages *in vitro*. The anti-CD47 antibody completely eliminated *in vivo* engraftment upon xenotransplantation into NOG mice. Finally, treatment of NOG mice already engrafted with human AML LSC with daily intraperitoneal injections of anti-CD47 antibodies for two weeks resulted in complete elimination of circulating leukaemia and a statistically significant reduction in bone marrow leukaemia.

Difference, its technical effect and problem to be solved

2.2 The claimed subject-matter differs from the closest prior-art document D16 in that it uses soluble human SIRPα or a CD47-binding fragment thereof (instead of anti-CD47 mAb) for treating haematological cancer cells that are CD47+ in a patient.

2.3 The patent shows, e.g. in Example 7, that *in vivo* intraperitoneal injection of soluble human SIRPα-Fc fusion protein decreases engraftment of human AML cells in bone marrow and spleen of mice after *intra*-femoral injection of the human AML cells.
There are no comparative data comparing the effects of soluble SIRPα molecules *versus* anti-CD47 antibodies.

2.4 Consequently, the board considers that the objective technical problem can be seen as the provision of an alternative compound capable of blocking the CD47-SIRPα interaction for treating CD47+ haematological cancer cells in a patient.

Obviousness

2.5 The crucial issue for the assessment of obviousness in the current case was to establish whether at the priority date the effect(s) caused by the interruption of CD47-SIRPα signalling was sufficiently established in light of the prior-art documents discussed by the parties.

2.5.1 A reported function of the CD47-SIRPα signalling complex is to prevent phagocytosis of red blood cells, platelets or leukocytes expressing CD47 as a "marker of self" by SIRPα-positive macrophages (see documents D6, page 3, paragraph 1; D7, page 459, right-hand column, paragraphs 1 and 2; D8, page 1320, left-hand column, first full paragraph; D12, see abstract and page 5063, left-hand column, paragraph 1; D13, page 74, right-hand column, last paragraph Figure 2a).

Both CD47 and SIRPα are reported to provide intracellular signals and may be present on the same cells such as macrophages. The level of expression of each protein is therefore crucial in determining the functional outcome of the interaction (see document D7, page 459, right-hand column, paragraphs 1 and 2).

2.5.2 However, the CD47-SIRPα interaction is also consistently described to play a role in multiple important leukocyte functions, including neutrophil and monocyte migration, macrophage recognition and apoptotic cell clearance, monocyte/macrophage fusion, T-cell and dendritic cell functions (see document D1, page 2, end of second full paragraph).

Anti-CD47 antibodies were reported to have anti-inflammatory and immune-suppressive effects suppressing

the release of inflammatory mediators such as IFNγ, allogenic mixed lymphocyte reaction (MLR), maturation of naive T-cells into pro-inflammatory Th1 cells and IgE synthesis (see document D4, page 5, lines 4 to 12; page 10, lines 24 to 31; page 22, lines 28 to 30 and page 23, line 5 to page 24, line 18).

In line with these observations, document D18 discloses that soluble SIRPα1 fusion proteins as well as SIRPα/β-specific and CD47-specific mAb reduce T-cell proliferation in MLR and inhibit the induction of primary T-cell responses (see abstract). Figures 6 and 7F of document D18 show that soluble SIRPα1 extracellular domains (SIRPα1ex) are able to reduce T-cell proliferation in an MLR more efficiently than an anti-CD47 or anti-SIRPα/β antibody. The presence of the soluble SIRPα1ex protein (Figure 7F) almost completely abolishes the induction of antigen-specific CTL.

This appears to be in line with observations that SIRPα signals inhibit macrophage secretion of inflammatory cytokines, such as tumour necrosis factor (see document D8 page 1320, left-hand column, first full paragraph).

Anti-CD47 mAb, anti-SIRPα mAb, soluble CD47 and soluble SIRP-IgV have been described to inhibit the migration of neutrophils and monocytes (see document D1, abstract and last paragraph of discussion; document D13, page 74, left-hand column). This is also considered an indication of an anti-inflammatory effect.

Thus, based on the information provided in documents D1, D4, D8 and D18, the skilled person would have expected that interrupting the CD47-SIRPα interaction would result in anti-inflammatory and immunosuppressive

effects, which are not at all desirable in the treatment of cancer.

2.5.3 Another document that casts doubt on the suitability of soluble SIRPα for the treatment of haematological cancer cells is document D6, which relates to the modulation of the CD47-SIRPα interaction to enhance HSC engraftment. Accordingly, the interaction between human SIRPα and CD47 may be modulated by administering at least one of a polypeptide capable of binding to the extracellular domain of human SIRPα or to the extracellular domain of human CD47 (such as soluble SIRPα) or anti-SIRPα or anti-CD47 antibodies (see page 17, last paragraph to page 18, second paragraph). Examples 14 and 15 of document D6 focus on SIRPα signalling and suggest that treatment with protein or small molecule agonists of SIRP can promote engraftment of human HSC in settings of clinical transplantation. However, claims 1 to 16 of document D6 relate, *inter alia*, to human CD47 binding polypeptides (see claims 3 c) or 9), which according to claims 18 and 19 are used for increasing HSC engraftment resulting from suppression of macrophages.

2.5.4 From the above analysis of the various documents, it can also be concluded that the skilled person knew that soluble SIRPα could be used as an alternative to anti-CD47 antibodies for blocking the CD47-SIRPα interaction. However, the documents discussed are not primarily concerned with providing a treatment for cancer and do not allow the conclusion that soluble SIRPα would be functionally equivalent to an anti-CD47 antibody in the treatment of haematopoietic cancers.

Document D16 does not disclose whether the anti-CD47 antibody used was an agonistic or antagonistic

antibody. Although in both cases the interaction between CD47 and SIRPα is blocked (i.e. signal transduction in SIRPα-expressing cells is prevented), an agonistic anti-CD47 antibody or soluble SIRPα induces, contrary to an antagonistic antibody, CD47 signalling in CD47+ cells and, thus, possibly has an effect that goes beyond the inhibition of the CD47-SIRPα interaction. The observation made in document D18 that a soluble SIRPα extracellular domain (SIRPα-ex) has more potent inhibitory effects on T-cells compared to inhibitory anti-CD47 antibodies (see Figures 6 and 7F) also indicates that soluble SIRPα might not act exactly the same as an inhibitory anti-CD47 antibody.

2.5.5 Hence, both the anti-inflammatory/immunosuppressive (see point 2.5.2 above) and HSC transplant-promoting effects reported in document D6 for soluble SIRPα suggest that it promotes rather than reduces cancer cell survival and consequently cast doubt on whether effective treatment of haematological cancers can be achieved.

2.6 The board considers that on the basis of these considerations, a skilled person did not have a reasonable expectation of success that soluble SIRPα can be successfully used in treating haematological cancers.

2.7 Starting from document D16 as the closest prior art and taking into account the teaching of the other documents cited above, the claimed subject-matter was not obvious to a skilled person.
The claimed subject-matter is therefore considered to involve an inventive step within the meaning of Article 56 EPC.

2.8 The teachings of documents D19, D48 and D51 were not considered relevant for assessing inventive step of the claimed subject-matter.

Document D19 was published after the priority date of the patent and is not prior art available to the skilled person at the priority date of the patent.

Document D48, which was also referenced in the discussion of inventive step, is not considered relevant because it examines the effects of SIRPα on presynaptic organisation and not the haematopoietic system (see e.g. abstract).

The data reported in conference abstract D51 teaching that CD47-SIRPα interactions are part of a homeostatic mechanism that limits antibody-mediated killing of tumour cells appear to be supportive of the data reported in closest prior-art document D16. However, the focus is on antibody-mediated elimination of tumour cells and blockage of CD47-SIRPα interaction by antagonistic antibodies in conjunction with cancer therapeutic antibodies.

3. Remittal to the department of first instance - Article 111(1) EPC

As the decision under appeal did not deal with disclosure of the invention under Article 83 EPC, there are special reasons to remit the case to the opposition division for further prosecution, as requested by all parties (Article 11 RPBA).

Order

For these reasons it is decided that:

- The decision under appeal is set aside.

- The case is remitted to the opposition division for further prosecution.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated