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Datasheet for the decision of 16 February 2023

Case Number: T 0654/20 - 3.3.04

Application Number: 07871350.0

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IPC: C07K16/28, A01N63/00

Language of the proceedings: EN

Title of invention:
Selective immunodepletion of endogenous stem cell niche for engraftment

Patent Proprietor:
The Board of Trustees of the Leland Stanford Junior University

Opponent:
Bosch Jehle Patentanwaltsgesellschaft mbH

Headword:
Stem cell immunodepletion/STANFORD UNIVERSITY

Relevant legal provisions:
EPC Art. 54(2), 56, 83, 123(2)
RPBA 2020 Art. 12(4), 12(6)

Keyword:

Amendments - added subject-matter (no)
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

T 1347/07

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Case Number: T 0654/20 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 February 2023

Appellant: (Opponent)	Bosch Jehle Patentanwaltsgesellschaft mbH Flüggenstr. 13 80639 München (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 DE-81925 München (DE)
Respondent: (Patent Proprietor)	The Board of Trustees of the Leland Stanford Junior University Office of the General Counsel Building 170, Third Floor, Main Quad P.O. Box 20386 Stanford, CA 94305-2038 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 January 2020 concerning maintenance of the European Patent No. 2088864 in amended form.**

Composition of the Board:

Chair	A. Chakravarty
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. An appeal was lodged by the opponent (appellant) against the decision of the opposition division to maintain European patent No. 1 734 997 in amended form. The patent is entitled "*Selective immunodepletion of endogenous stem cell niche for engraftment*". The patent is based on European patent application No. 07871350.0 published under the PCT as WO2008/067115 (the application).

II. The patent was opposed on the grounds in Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and in Articles 100(b) and 100(c) EPC.

III. In the decision under appeal, the opposition division decided that the main request (claims amended with letter of 11 October 2018) fulfilled the requirements of the EPC. In its decision, the opposition division held that document D3 was comprised in the state of the art due to a lack of a valid claim to priority because the claimed subject-matter did not relate to the same invention as the application from which priority was claimed. The filing date was therefore considered as the effective date. However, the opposition division dismissed an objection of lack of inventive step also when taking into account document D3.

IV. With the statement of grounds of appeal, the appellant maintained objections of lack of novelty and lack of inventive step against the subject-matter of claim 1 of the main request and against sufficiency of disclosure of the invention claimed thereby, but did not maintain its objections under Article 123(2) EPC concerning

added subject-matter. It further filed documents D54 to D57.

V. With its reply to the appellant's statement of grounds of appeal, the patent proprietor (respondent) re-filed sets of claims of the main request and auxiliary requests 1 to 25 filed during the proceedings before the opposition division. The respondent had "*no comments on the 'same invention' point*" with regard to the claimed priority, but maintained that "*formal priority entitlement should indeed be recognized*" (see point 4 of the reply). It further filed documents D58 and D59.

VI. With a letter dated 20 December 2021, the appellant replied to the response and filed document D60.

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

VIII. With a letter dated 16 January 2023, the respondent withdrew the main request and designated auxiliary request 11 as the main request. Former auxiliary requests 14, 12, 16, 24, 23, 19 and 25 were renumbered as auxiliary requests 1 to 7, respectively. All other auxiliary requests were withdrawn. It further filed document D61.

IX. Independent claim 1 of the main request reads as follows:

"1. A composition comprising an antibody that selectively binds c-kit and interferes with c-kit signaling essential for hematopoietic stem cell growth

or maintenance for use in a method of stem cell engraftment in a human severe combined immunodeficiency (SCID) patient, wherein the method comprises:
contacting said patient with said composition to selectively ablate endogenous hematopoietic stem cells in bone marrow; and
introducing exogenous hematopoietic stem cells to said patient after a period of time sufficient to substantially eliminate said antibody from the patient circulation,
wherein said exogenous hematopoietic stem cells are allogeneic or autologous hematopoietic stem cells, and wherein said period of time sufficient to substantially eliminate said antibody is such that the antibody is present at a concentration of less than 10 ng/ml in the bloodstream."

X. With a letter dated 3 February 2023, the appellant indicated that it would not attend the oral proceedings.

XI. Oral proceedings before the board took place on 16 February 2023 in the absence of the appellant, who relied on its written case (Article 15(3) RPBA). At the end of the oral proceedings, the Chair announced the board's decision.

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

D1 WO2004/002425 A2

D3 D. L. Kraft et al., "*196: Ability of anti c-Kit targeting monoclonal antibody ACK-2 to target hematopoietic stem cells, and facilitate engraftment of human CD34+ engraftment and hematolymphoid development in immunodeficient mice: A novel antibody based conditioning strategy*", Biology of Blood and Marrow Transplantation 13(2)Suppl., 2007, 72.

D32 A. Chhabra et al., "*Hematopoietic stem cell transplantation in immunocompetent hosts without radiation or chemotherapy*", Sci Transl Med 8(351), 2016, 1-22.

D34 W. W. Pang et al., "*Anti-CD 117 antibody depletes normal and myelodysplastic syndrome human hematopoietic stem cells in xenografted mice*", Blood 133(19), 2019, 2069-2078.

D43 J. M. Burke et al., "*Cytoreduction with iodine-131-anti-CD33 antibodies before bone marrow transplantation for advanced myeloid leukemias*", Bone Marrow Transpl 32(6), 2003, 549-556.

D45 A. Gouyette et al., "*Pharmacokinetics of high-dose melphalan in children and adults*" Cancer Chemother Pharmacol 16, 1986, 184-189.

D49 T. B. Moore and K. M. Sakamoto, "*Topics in Pediatric Leukemia - Hematopoietic Stem Cell Transplantation*", MedGenMed 7(1), 2005, 19.

D50 Declaration Prof. I. Weissman.

D61 Declaration Dr. A. Czechowicz and Annexes.

XIII. The appellant's arguments as far as relevant to the decision may be summarised as follows.

Main request (former auxiliary request 11)
Admittance (Article 12(4) RPBA)

Former auxiliary requests 1 to 25, including former auxiliary request 11, which has become the main request, should not be admitted because they were divergent in that they did not increasingly limit the subject-matter of claim 1 of the main request in the same direction (see Case Law of the Boards of Appeal, 10th edition 2022, V.A.4.12.4).

Claim construction

Claim 1 required that the antibody bound c-kit and interfered with c-kit signaling. Claim 1 further required that the composition comprising this antibody selectively ablated endogenous hematopoietic stem cells in bone marrow. There was nothing in the claim that implied that c-kit interference was responsible for the ablation of HSCs. This was a further functional limitation of the antibody which could not be found in the claim. The claim was also not restricted to antibodies that completely (and not only partially) inhibited c-kit signaling. Claim 1 thus encompassed any anti-c-kit antibody that interfered with c-kit signaling.

Amendments (Article 123(2) EPC)

The application did not provide basis for generalising to a human SCID patient.

Disclosure of the application (Article 83 EPC)
Antibody therapy in humans

The opposed patent did not disclose an antibody targeting a human antigen, since the ACK2 antibody targeted murine CD117 (see document D1, Table 3.1). The opposed patent thus also did not contain data demonstrating safety or efficacy of treatment in humans.

The antibody definition covers non-working embodiments

According to the patent, Fab fragments that bound c-kit and interfered with c-kit signaling selectively ablated endogenous HSCs in a human patient. Document D32 showed that this did not work. The Fab fragment of ACK2 used in document D32 could be expected to inhibit binding and thus interfere with c-kit signalling because antibodies bound via their Fab part. Fab fragments were still able to interfere with c-kit signaling but could not ablate endogenous HSCs, because they lacked an Fc domain. The doubts about Fab fragments based on document D32 were not overcome by the disclosure in document D34 which showed that another antibody, SR-1, in a glycosylated form, was able to ablate HSCs. The opposed patent provided no guidance which allowed the skilled person to identify antibodies other than ACK2 which were suitable to ablate HSCs. Furthermore, it was apparent from the patent that weakly interfering antibodies such as 2B8 were not suitable to ablate endogenous HSCs (see Figure 2C and paragraph [0096]).

The threshold at which point interference with c-kit signaling became therapeutically relevant was not derivable from the opposed patent.

Novelty (Article 54 EPC)

Document D1 disclosed a method involving the conditioning of a human patient with a "*therapeutic composition of the present invention (TC), such as for example anti-CD117*" (page 45, lines 23 to 25; page 48, lines 15 to 26) "*followed by allogeneic mobilized peripheral hematopoietic stem cell (MPHSC) transplant*" (page 48, lines 4 to 6). In other words, document D1 disclosed the therapeutic use of an antibody binding to and antagonising c-kit (also known as CD117).

Antibody SR-1 disclosed in document D1 was an antibody for use in humans since it targeted human c-kit.

It was directly and unambiguously derivable that antibody SR-1 would have to be humanised in accordance with the teaching in document D1 before it could induce a complement response using human serum. This involved only routine techniques. The skilled person would derive from document D1 that SR-1 was a promising antibody for humanisation given that it was capable of depleting c-kit expressing human cells in the presence of a complement system which was compatible with its murine Fc domain, i.e. rabbit complement.

The humanisation of antibody SR-1 was directly and unambiguously derivable from the disclosure of document D1 because:

i) Example 2 disclosed a method of engrafting HSCs in human patients "*using the therapeutic composition(s) of the present invention*" (page 46, lines 27 to 29);
(ii) SR-1 was disclosed as being an antibody that could be used in the compositions of the invention (page 37, lines 1 to 6);
(iii) SR-1 was the only human c-kit targeting antibody that depleted stem cells in a similar fashion to 2B8 (page 68, line 27 to page 69, line 2);
(iv) SR-1 could only lyse the c-kit expressing cells in the presence of rabbit complement but not in the presence of human serum (Figure 16);
(v) complement-mediated cell killing was at least partially responsible for cell ablation (page 68, lines 12 to 15);
(vi) SR-1 had a mouse IgG2a isotype (Table 8.1);
(vii) it was common general knowledge that human constant regions allowed more efficient interaction with human complement-dependent cytotoxicity (D56: page 5, paragraph 1); and
(viii) humanised antibodies were disclosed as being particularly useful (page 6, lines 1420).

Document D1 also provided a direct and unambiguous disclosure for a step wherein the exogenous HSCs were introduced after a period sufficient to clear the antibody from the patient circulation as recited in claim 1. Instructions to wait until the excess antibody was cleared (see Example 2, page 48, lines 24 to 26) or the antibody was substantially cleared (see page 29, lines 24 to 28 and page 36, lines 2 to 3), would have inherently guided the skilled person to wait until the concentration of the antibody in the bloodstream was 10 ng/ml or less because the term "cleared" directly and unambiguously implied or at least included a concentration of 0 ng/ml.

The subject-matter of claim 1 thus lacked novelty.

Inventive step (Article 56 EPC)
Starting from document D1

The objective technical problem was the provision of an alternative engraftment method. It would have been obvious to develop a humanised variant of SR-1 for use in the method disclosed in Example 2. The skilled person would have chosen SR-1 for the development of a therapy in humans because it was the most promising anti-human c-kit antibody disclosed in document D1. Thus, even if there was an unexpected technical effect associated with blocking c-kit signaling for the ablation of antibodies, this should be considered a "bonus effect" because it would have been obvious to arrive at something falling within the terms of claim 1 in view of document D1.

A skilled person who was considering performing pre-clinical HSC engraftment experiments in a mouse would first have determined whether such experiments using any of the antibodies described in document D1 had already been described. The skilled person would then have found document D3, which described such an experiment. Document D3 provided evidence that ACK2, an antibody that was used in document D1 and was known to interfere with c-kit signaling (see document D1, page 56, lines 17 to 20), was able to ablate endogenous stem cells in an immunocompromised mouse. Thus, the skilled person would have used a c-kit interfering antibody for ablating endogenous stem cells in a human patient in view of the promising results for SR-1 in document D1 and for ACK2 in document D3.

Document D1 already disclosed the concept of waiting until the antibody was cleared before administering HSCs. Leaving a certain amount of time between administration of the conditioning agent and the HSC transplantation would also have been obvious to the skilled person because this practice was well established in the field of conditioning for HSC transplantation (see documents D43, D47 and D49). Furthermore, there was no technical effect associated with the clearance level of less than 10 ng/ml. This feature was arbitrary and a matter of common sense.

Starting from document D3

The objective technical problem might be seen in the translation of the animal model data in document D3 into clinical practice for human patients. Document D3 disclosed that experiments involving ACK2 conditioning had been performed, engraftment with donor murine HSCs was achieved, as supported by the additional xenograft data. The skilled person would have had no reason to consider that it was not credible that the ACK2 conditioning alone would enable donor murine HSC engraftment.

Thus, starting from document D3 it would be obvious to develop the claimed therapy in view of document D1 and common general knowledge. The skilled person would merely have aimed to develop the human therapy disclosed in document D1, Example 2 on the basis of the promising results obtained in document D3 using nothing more than routine methods. The skilled person would have chosen SR-1 as the basis for developing therapies in humans because, unlike ACK2, SR-1 targeted human c-kit. Furthermore, SR-1 was both a blocking ligand and was considered promising for depletion of stem cells in

document D1 because it resulted in complement-mediated cell lysis (see page 68, line 27 to page 69, line 2). Thus, the skilled person would have had no reason to doubt that SR-1 would work.

The skilled person, with his or her common general knowledge and being aware of the data obtained with the model of document D3, would have had at least a reasonable expectation that an anti-c-kit antibody that bound and interfered with c-kit signaling would also be suitable for conditioning humans for autologous or allogeneic HSC engraftment. It was common general knowledge that previous conditioning regimens were also based on animal models developed to achieve stable mixed hematopoietic chimerism such as the model provided in document D3 (see document D54, page 115, left column, paragraph 2).

The claimed subject-matter thus lacked inventive step over the disclosure of documents D1 or D3 alone or in combination (Article 56 EPC).

XIV. The respondent's arguments as far as relevant to the decision may be summarised as follows.

Main request (former auxiliary request 11)
Amendments (Article 123(2) EPC)

The application as filed disclosed the treatment of human SCID patients in paragraphs [86] and [119]. This disclosure was in the context of transplantation of exogenous stem cells (see paragraph [71]. Already in the general introduction, paragraph [15] made reference to "severe immunodeficiency". The general disclosure of SCID in paragraph [86] could thus be combined with

further features of the invention without adding subject-matter.

Sufficiency of disclosure (Article 83 EPC)

The patent provided credible support for using an anti-c-kit blocking antibody in a method of human HSC engraftment in a human patient. Antibody AMG 191, a humanised version of the SR-1 antibody was capable of depleting human HSCs and facilitating allogeneic HSC engraftment, even though this anti-human c-kit antibody was not recognised by Fc receptors (see post-published document D34).

Antibody 2B8, referred to in the patent, was an anti-mouse c-kit antibody that did not bind to human c-kit. Therefore, antibody 2B8 was not encompassed by the definition in claim 1, and so could not represent a non-working embodiment of the claims. No sufficiency issue arose from the fact that antibody 2B8 demonstrated weak antagonism *in vitro* and could not be used to deplete HSCs *in vivo*. The patent taught the skilled person that the reason that 2B8 was ineffective in depleting HSCs was because it provided only modest interference with c-kit signalling. Accordingly, the skilled person would understand from the patent itself that a higher level of antagonism was required to achieve HSC depletion *in vivo*. There was no undue burden associated with screening anti-c-kit antibodies to assess the strength of their antagonistic activity. This involved performing an *in vitro* proliferation assay (see e.g. Figure 2E of the patent). The recited therapeutic effect resulted in the exclusion of antibodies that were not capable of ablating endogenous HSCs, even if these antibodies detectably antagonised c-kit signalling. There was no undue burden associated

with identifying those antagonistic anti-c-kit antibodies that could be used to implement the claimed therapy.

Novelty (Article 54 EPC)

Antibody SR-1 was a mouse IgG2a antibody (see page 65, lines 22 to 23 of document D1), which the skilled person would have considered as not appropriate for human therapy, in view of the human anti-mouse antibody (HAMA) response. The skilled person would have concluded that SR-1 was incapable of depleting HSCs in human subjects because it had a mouse Fc region which, according to the teaching of document D1, required a compatible complement for the ablation of HSCs (see Figure 17B of document D1). Document D1 did not disclose treatment of human subjects with SR-1, but even if it did, this would not constitute a disclosure of treatment of human subjects with humanised SR-1.

The opposition division was correct to conclude that "*no particular clearance level within the terms of claim 1 can be directly and unambiguously derived from D1*". The disclosures in Example 2, page 29 and page 36 were unclear or did not relate to anti-c-kit antibodies.

Even if the individual features of 1 were considered to be disclosed in document D1, the combination of these features was not directly and unambiguously derivable from the document.

Inventive step (Article 56 EPC)
Starting from document D1

The most appropriate starting point for the assessment of inventive step was Example 2 of document D1. There were two differences between this disclosure and the subject-matter in the claim: i) the antibody interfered with c-kit signalling and ii) the exogenous HSCs had to be introduced after a period of time sufficient to substantially eliminate said antibody such that the antibody was present at a concentration of less than 10 ng/ml in the bloodstream. These two differences contributed to the technical effect of increased HSC engraftment, in the context of allogeneic or autologous human therapy. Therefore, the objective technical problem was correctly formulated by the opposition division as the provision of an improved method of HSC engraftment in allogeneic or autologous human therapy.

There was no suggestion in the prior art to use an interfering anti-c-kit antibody to achieve an improved therapy. There was also no clear pointer to the "*period of time*" embodied in the less than 10 ng/ml cut-off in claim 1. Furthermore, there was no reasonable expectation of success for the method of Example 2 of document D1, let alone an expectation of improvement through the modifications required to reach the claimed therapy.

Starting from document D3

Document D3 did not disclose any of: (1) the treatment of human patients, (2) the administration of autologous or allogeneic HSC, or (3) waiting a period of time until the anti-c-kit antibody has fallen below 10 ng/ml.

Document D3 indicated that the capability (or lack thereof) of ACK2-mediated same-species HSC engraftment would be reported in the future. The "CONCLUSIONS" section of D3 was silent on the possibility of donor murine HSC engraftment, in contrast to the reported success of "human CD34+ engraftment", such that the skilled person could not have drawn any conclusion from document D3 regarding the possibility of donor murine HSC engraftment.

The objective technical problem might therefore be formulated as the provision of an effective method for achieving successful allogeneic or autologous HSC in a human patient.

The skilled person starting from document D3 would have had no reason to expect there to be a 'window of opportunity' in which the level of anti-c-kit antibody was sufficiently low and the bone marrow niches were sufficiently vacant to enable engraftment of donor HSCs from the same species. Indeed, the only attempt in the cited prior art was in document D24, which resulted in failure. There were no examples of success for similar methods in the common general knowledge.

If the skilled person had contemplated combining the disclosure of document D3 with that of document D1 they would have faced other difficulties. Firstly, contradictory information was provided with regard to whether ACK2 was capable of depleting mouse HSCs *in vivo*. While document D3 stated that ACK2 was capable of depleting mouse HSCs, document D1 reported that mouse HSCs were "refractory" to ACK2 treatment (see page 68, lines 5 to 7). Secondly, there was no coherent teaching in document D1 with respect to antibody clearance. "Excess" antibody in the serum at the time of donor HSC

administration was presented in document D1 as both a goal (see page 39, lines 5 to 8) and something to be avoided (see page 48, lines 24 to 26). Thirdly, while document D3 noted that ACK2 was an antibody "*which had been shown to antagonize the function of c-kit*", document D1 taught that this functional property was irrelevant and that anti-c-kit antibodies depleted HSCs through complement activation (see paragraph bridging pages 67 and 68). Prof. Weissman in document D50 confirmed that "*before the experiments reported in the patent, there had been no report in the literature of successfully preparing a recipient for an autologous or allogeneic HSC transplant by administering any antibody (for any antigen)*".

The claimed subject-matter was inventive (Article 56 EPC).

XV. The appellant requests that the decision of the opposition division be set aside and the patent be revoked. Moreover,
- documents D54 to D57 and D60 should be admitted into the proceedings;
- auxiliary requests 1 to 3, 6 to 8, 13, 14, 18 to 20, 22, 23 and 25 should not be admitted into the proceedings because the amendment made to claim 1 of these requests (to recite a pharmaceutical composition) was not an amendment occasioned by a ground for opposition;
- auxiliary requests 1 to 25 should not be admitted into the proceedings because they were divergent.
Furthermore, document D61 which was late filed and not *prima facie* relevant should not be admitted into the proceedings. The respondent's argument that document D1 was not an enabling disclosure came at a late stage and should not be admitted into the proceedings.

The respondent requests that the decision of the opposition division be set aside and the patent be maintained in amended form on the basis of the main request (former auxiliary request 11); or alternatively on the basis of any of auxiliary requests 1 to 7 (former auxiliary requests 14, 12, 16, 24, 23, 19 and 25, respectively). Furthermore, document D61 should be admitted into the proceedings.

Reasons for the Decision

Main Request
Admittance (Article 12(4)(6) RPBA)

1. The appellant argued that none of the auxiliary requests 1 to 25 should be admitted into the proceedings because they were "*divergent in that they do not develop an* [sic] *increasingly limit the subject matter of claim 1 of the Main request in the same direction*". Since auxiliary request 11 became the main request there is no issue of limitation in the same direction and this argument is moot.

2. The main request was filed on 11 October 2019 as auxiliary request 11, i.e. after the expiry of the time limit set by the opposition division under Rule 116(1) EPC. The patent proprietor at that time reasoned that the limitation to the treatment of human severe combined immunodeficiency (SCID) patients of the claims was occasioned by new submissions of the opponent. The request was not dealt with in the decision under appeal because a higher ranking request (the then main request) was found allowable. The amendment addresses an issue of sufficiency of disclosure for which the opponent had submitted new evidence shortly before the final date set out

according to Rule 116(1) EPC. It represents a reaction which could not have been filed earlier.

3. The board therefore decided to admit the request into the proceedings under Article 12(6) RPBA.

Claim construction

4. The board agrees with the opposition division in the decision under appeal that the claim requires that the selective ablation of endogenous hematopoietic stem cells in bone marrow is caused by the antibody which binds to c-kit and interferes with c-kit signalling (see point 3.8 of the decision), while other mechanisms (such as Fc-function) can contribute to the ablation (see point 4.8 of the decision). The antibody has to be suitable for use in human patients, i.e. it has to bind and interfere with human c-kit.

5. The term "antibody" is defined in the patent as including antibody fragments (e.g. Fab) which lack an Fc region (see paragraph [0025]). Since this is a technically sensible definition of the term, the board sees no reason not to adopt it when interpreting the claim.

Claim 1
Amendments (Article 123(2) EPC)

6. The appellant objected to the amendment of the claim to include the feature "a human severe combined immunodeficiency (SCID) patient" because it extended the subject-matter beyond the content of the application as filed.

7. Paragraph [86] in the application as filed, which was referred to by the appellant, discloses that "*combined immunodeficiencies include severe combined immunodeficiency*". This is in the context of embodiments of the invention which "include *transplantation into a patient suffering from a genetic blood disorder, where exogenous stem cells of a normal phenotype are transplanted into the patient*" (see paragraph [71]). "*Severe immunodeficiency*" is also mentioned in paragraph [15], relating to hematopoietic stem cell treatment. The selection of SCID involves only a selection from a single list of diseases (see paragraphs [15] and [86]). Since the treatment of human patients is a preferred embodiment of the application as filed, no further selection or combination is required.

8. The amendment therefore does not contravene the requirements of Article 123(2) EPC.

9. The appellant did not maintain any other objections under Article 123(2) EPC (see section XIII.).

Disclosure of the invention (Article 83 EPC)
Therapy of human SCID patients

10. The appellant argued that the application as filed did not make it credible that the claimed HSC conditioning therapy could be carried out in humans because the experiments reported in the patent had only been performed in mice with the antibody ACK2, which bound mouse but not human c-kit. The patent contained no data demonstrating the safety or efficacy of any treatment in humans.

11. The experiments performed in mice show ablation of endogenous HSCs and successful engraftment of donor HSCs from the same species (see paragraph [102]) as well as an improvement of chimerism compared to untreated control animals (see Figure 3A). They furthermore identify sufficient antibody clearance as relevant for successful engraftment (see paragraph [92]). The underlying mechanism (interference with c-kit signalling to ablate HSCs) is the same between the mouse model and human patients. It can thus be reasonably assumed that the claimed compound has a direct effect on the metabolic mechanism specifically involved in the therapeutic use and that the findings can be transferred from mice to humans.

Identifying suitable antibodies

12. The appellant was of the view that antibodies lacking an Fc region were not capable of ablating HSCs because the Fc region was known from document D32 to mediate said ablation. Thus document D32 proved that the claim did not meet the requirements of Article 83 EPC.

13. The opposition division dismissed this argument because it considered that document D32 did not prove that the ACK2 Fab fragment interfered with c-kit signalling at all, i.e. it was not clear whether it was an antibody as defined in the claim (see point 4.9 of the decision).

14. The board does not agree with the opposition division's reasoning because it was common general knowledge that antibodies bind their target through the CDRs in the Fab portion, thus a Fab fragment of antibody ACK2 must also bind to c-kit and interfere with c-kit signaling by preventing the binding of the c-kit ligand pSCF (see

also document D1, Table 3.1 for the ligand binding activity of ACK2).

15. Document D32 therefore supports the idea that the Fc portion of an antibody may be required for it to be useful in the ablation of HSCs. This is confirmed in document D50 by Prof. Weissman, one of the authors of document D32, who states: "*our experiments showed that ACK2-mediated HSC clearance is dependent on its Fc portion*" (see point 12).

16. On the other hand, document D34 shows that the aglycosylated antibody SR-1 (which is not recognised by Fc receptors) is capable of depleting human HSCs in humanised mice.

17. The evidence in documents D32 and D34 taken together leads the board to conclude that, while the Fc region contributes to the HSC ablating function of some antibodies, it is not always required for this function.

18. The respondent pointed out that the antibody defined in the claim not only had to selectively bind c-kit and interfere with c-kit signaling essential for hematopoietic stem cell growth or maintenance but also had to selectively ablate endogenous hematopoietic stem cells in bone marrow (see claim construction in point 4. above). The skilled person would thus also test the antibody for this latter functionality, employing the assays disclosed in the patent (see e.g. paragraphs [14] and [36]) and would thus be able to exclude non-working embodiments without undue burden.

19. The appellant further referred to antibody 2B8 which partially interfered with c-kit signalling and thus

fell under the scope of the claim under "*the broadest reasonable technical interpretation*" (see appellant's letter of 20 December 2021, page 7), but was not suitable for ablating HSCs (see Figure 2C and paragraphs [0017] and [0096]).

20. Under the claim construction adopted by the board (see point 4. above), antibody 2B8 which binds mouse as opposed to human c-kit is not covered by the functional definition in the claim because "selectively binds c-kit and interferes with c-kit signaling essential for hematopoietic stem cell growth or maintenance" in the context of a medical use in humans, must relate to binding and interfering with human c-kit. The fact that the 2B8 antibody does not ablate HSCs is thus immaterial to the question of sufficiency of disclosure of the invention to which the patent relates.

21. Even if it could be concluded from the example of antibody 2B8 that (partial) interference with c-kit signalling alone is not sufficient to predict whether an antibody is capable of ablating HSCs, the patent discloses further assays with which the skilled person can select antibodies capable of ablating HSCs without undue burden (see point 18. above).

22. In conclusion, the invention is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art(Article 83 EPC).

Novelty (Article 54 EPC)

23. The opposition division found that the subject-matter of claim 1 of the then main request did not lack novelty because document D1 failed to disclose (i) a therapeutic use of an interfering antibody against c-

kit in humans and (ii) transplanting of HSCs after the antibody was present at a concentration of less than 10 ng/ml.

24. The board agrees with the first finding of the opposition division because document D1 neither contains an explicit disclosure of a therapeutic use of antibody SR-1 in humans nor does it contain evidence derived from *in vivo experiments* (e.g. from an animal experiment) that an antibody binding to c-kit and interfering with c-kit signalling (e.g. SR-1) leads to the selective ablation of endogenous stem cells and the engraftment of exogenous allogeneic or autologous stem cells. Attaining this therapeutic effect, however, is a functional feature of the medical use claim under consideration. The requirements of sufficiency of disclosure are identical for a prior art document and a patent (see decision T 1347/07, point 25 of Reasons).

25. In document D1 two antibodies (2B8 and 3C1) which do not interfere with binding of the c-kit ligand were used to test *in vivo* ablation of endogenous stem cells (see page 57, lines 6 to 9 and Table 3.1). Subsequent transplantation and engraftment of stem cells was not tested for any of the antibodies.

26. In document D1, antibody SR-1, which binds to and interferes with human c-kit, but is of a mouse IgG2a isotype, was only tested in an *in vitro* "Cobblestone Area-forming Cell" (CAFC) assay together with rabbit complement (see Example 11 on page 67, lines 16 to 20). The board agrees with the expert opinion in document D50 that the skilled person would have considered the CAFC assay not suitable to render credible the successful ablation of endogenous HSCs and engraftment

of allogeneic or autologous HSCs (see document D50, points 15 to 28).

27. Furthermore, in view of the commonly known human anti-mouse antibody (HAMA) response, antibody SR-1, which has a mouse Fc region, is not suitable for human therapy. Moreover, according to the teaching of document D1, antibody SR-1 requires a compatible complement for the ablation of HSCs, which is not present in human patients (see Figure 17B of document D1). Document D1 thus does not disclose a medical use in humans of the SR-1 antibody.

28. The board does not agree with the appellant's argument that the skilled person would have considered a humanised version of the SR-1 antibody as directly and unambiguously derivable from the disclosure of document D1. Document D1 contains no direct disclosure in this regard, but only a general disclosure that antibodies can be humanised (see page 6, line 15 and page 11, line 11). Document D1 thus also does not disclose a medical use in humans of a humanised version of the SR-1 antibody.

29. The board also agrees with the opposition division's second finding that document D1 does not disclose transplanting of HSCs after the antibody was present at a concentration of less than 10 ng/ml. The sections cited by the appellant either relate to general statements such as, "*dose and/or timing of administration of the agent should not affect the concentration of donor stem cells administered*" (see page 29, lines 24 to 25) or "*as long as excess antibody has been cleared from the circulation*" (page 49, lines 23 to 26), or they relate to other treatment options such as anti-T-cell (e.g. anti-CD4, anti-CD8)

antibodies (see page 29, lines 25 to 28) or a combination of anti-T-cell antibodies and anti-PHSC (peripheral hematopoietic stem cell) antibodies (see page 36, lines 2 to 3).

30. The appellant's argument that a value of 0 ng/ml, i.e. no antibody, was implicit in the disclosure of document D1 is not convincing because the relative terms such as "cleared" or "excess" used in document D1 do not mean that a value of 0 ng/ml of antibody had to be reached. A specific range of concentrations of less than 10 ng/ml in the bloodstream, as defined in the claim, is not disclosed in document D1.

31. The appellant did not maintain any objections of lack of novelty vis à vis any other disclosure in the state of the art.

32. The claimed subject-matter is novel (Article 54 EPC).

Inventive step (Article 56 EPC)
Closest prior art

33. In the decision under appeal, document D1 was considered to be the closest prior art for the claimed subject-matter. The appellant proposed document D3 as an alternative starting point. Inventive step is therefore assessed starting from both document D1 and document D3.

Document D1 as starting point

34. The opposition division was of the opinion that "*already selecting the specific SR-1 embodiment from the various embodiments of D1 is an indication of inadmissible ex post facto analysis*". The board does

not agree because according to Article 56 EPC an invention should not be obvious to the skilled person, having regard to the state of the art. The board thus considers it immaterial which embodiment in document D1 is taken as the starting point for an inventive step analysis. It therefore uses antibody SR-1 as the starting point for analysing inventive step, as suggested by the appellant.

Difference and objective technical problem

35. Document D1 discloses antibody SR-1 which binds to human c-kit and interferes with human c-kit signalling. This antibody is proposed for "*depleting and/or inactivating hematopoietic stem cells in the recipient*" (see page 37, lines 1 to 7). The antibody is, however, of a mouse IgG2a type and thus not directly suitable for human therapy (see point 27. above). A first difference between the claimed subject-matter and the disclosure in document D1 is thus the suitability of the antibody for human therapy.

36. A second difference between the claimed subject-matter and the disclosure of document D1 is that the exogenous HCSs are introduced after a period of time sufficient to eliminate the antibody such that it is present at a concentration of less than 10 ng/ml in the bloodstream (see point 29. above).

37. The technical effect of these differences is at least two-fold:
(1) suitability of the antibody for use in human patients;
(2) improved HSC engraftment due to the clearance of antibody.

38. In view of the above differences between the closest prior art and the claimed invention and the technical effect thereof, the objective technical problem can be formulated as the provision of an improved method to allow engraftment of allogeneic or autologous HSCs in human SCID patients.

Obviousness

39. The question to be asked in assessing the obviousness of the claimed subject-matter is whether or not the skilled person, starting from the disclosure in document D1 and seeking to provide an improved method for engraftment of autologous or allogeneic HSCs in human SCID patient, could and would have provided the claimed composition for the claimed use. The skilled person reading document D1 would have concluded that c-kit signalling was not relevant for ablation of HSCs. Although antibody SR-1 (which does bind to human c-kit and interferes with human c-kit signalling) was found in the *in vitro* CAFC assay to "*selectively deplete stem cells in a similar fashion to the 2B8* [antibody]" (see page 68, lines 29 to 32) this was attributed to its complement-mediated cell lysis activity and not to its ligand blocking activity (see page 68, lines 16 to 24) which was considered "*not a characteristic that predisposes the cells to complement-mediated cell lysis*" (see page 68, lines 22 to 24). Antibody SR-1 or any other antibody interfering with c-kit signalling disclosed in document D1 were also not used in *in vivo* experiments to show that the antibody was indeed able to ablate endogenous HSCs and free the respective stem cell niches for donor cell transplantation. This would have indicated to the skilled person that these antibodies were considered less promising. Document D1 thus contains no evidence that antibodies that bind to

human c-kit and interfere with the signalling of human c-kit in this way exert a therapeutic effect.

40. In contrast, antibody 2B8, which according to document D1 did not interfere with c-kit signalling (see Table 3.1) was used in *in vivo* experiments (see page 57, lines 6 to 9 and Examples 4 to 6). These experiments showed that "*the 2B8 MAb that is incapable of inhibiting SCF binding had the most promising effect in preferentially depleting the late-forming CAFC subsets*" (see page 68, lines 7 to 15). In conclusion, on page 68, lines 1 to 10, it is stated that "*inhibition of binding of the c-kit ligand is a* [sic] *not a prerequisite for these antibodies to deplete hematopoietic stem cells*".

41. In the board's view, the disclosure of document D1 as a whole would have lead the skilled person to focus on those antibodies which were presented as preferred therein, in particular antibody 2B8 for HSC engraftment therapy in human SCID patients. Even if the skilled person had pursued the development of the SR-1 antibody for human therapy, e.g. by humanisation, there was no reasonable expectation that this would be successful. Indeed, only *in vitro* experiments with an assay that the skilled person would have considered insufficient to establish HSC engraftment (see document D50, points 15 to 34) had been performed in document D1. Moreover, the importance of antibody clearance to a very low level had not been recognised in document D1 (see point 29. above) and the skilled person had no reason to adapt the conditioning method disclosed in document D1 in this respect. There was therefore no incentive or motivation for the skilled person to modify antibody SR-1 to make it suitable for use in humans, or to check

its clearance in the bloodstream before transplanting allogeneic or autologous HSCs.

42. The appellant also argued that the claimed subject-matter would have been obvious to the skilled person starting from the disclosure in document D1, when considered in combination with that in document D3. The board is not persuaded by this line of argument either because document D3 does not relate to the antibody SR-1 for human SCID therapy, but concerns the mouse c-kit antibody ACK2 in the development of a mouse model. It does not relate to allogeneic or autologous transplantation nor is it concerned with the level of antibodies in the bloodstream before transplanting HSCs.

43. In view of the above considerations, the board concludes that the skilled person seeking to solve the technical problem formulated above and starting from the disclosure in document D1 would not have arrived in an obvious manner at the claimed subject-matter, which therefore involves an inventive step with respect to the disclosure of document D1, alone or in combination with the disclosure of document D3.

Document D3 as starting point

44. Document D3 discloses engraftment of human CD34+ HSCs in sublethally irradiated immunodeficient mice (i.e. xenogeneic transplantation) after ablation of endogenous HSCs with the ACK2 antibody which binds to mouse c-kit and interferes with mouse c-kit signalling. The document states that anti c-kit mAb treatment "*may serve as a strategy for host HSC targeted mAb based conditioning*". It concludes that ACK2 "*may serve as a means to enhance this new model of human*

hematopoiesis". The reference to "*the ability for host ACK2 conditioning alone* [i.e. without irradiation] *to enable donor murine* [i.e. allogeneic] *HSC engraftment will be presented*" (underlining by the board) apparently refers to the poster session for which the document represents the abstract.

45. The board considers that any disclosure made at said poster session, in particular, reference to potential future findings, is not part of the disclosure of document D3 and is not part of the state of the art for the patent because it is not clear what was presented at the poster session, when, or in which form, e.g. orally or written, and with which detail. As correctly pointed out by the respondent, because of the future tense used in the statement, it is not even clear from document D3 whether the outcome of the experiments "*for host ACK2 conditioning alone to enable donor murine HSC engraftment*" was positive or negative.

Difference and objective technical problem

46. The differences between the claimed subject-matter and the disclosure in document D3 thus lie in (i) the treatment of a human SCID patient instead of irradiated immunodeficient mice, (ii) the use of an antibody targeting human c-kit and suitable for human therapy instead of mouse c-kit antibody ACK2, (iii) the engraftment of allogeneic or autologous HSCs instead of xenogeneic human HSCs and (iv) the clearance of antibodies from the bloodstream to at least 10 ng/ml, whereas antibody clearance is not disclosed in document D3. The technical effects of differences (i) to (iv) are:

- suitability of the method for the treatment of human SCID patients, of difference

- better immuno-compatibility, and
- improved HSC engraftment due to the clearance of the antibody.

47. The objective technical problem resulting from the above mentioned differences and the technical effects thereof is the same as that formulated when starting from document D1, namely, the provision of an improved method to allow engraftment of allogeneic or autologous HSCs in human SCID patients.

Obviousness

48. The skilled person starting from the disclosure in document D3 would not have known whether the results of experiments performed with xenogeneic engraftments could be transferred to an allogeneic or autologous setting. It was also not clear from the disclosure in document D3 whether the ACK2 antibody alone, i.e. without sublethal irradiation was sufficient to achieve the conditioning. Finally, the skilled person would have found no information in document D3 about the clearance of antibody before engraftment and thus the timing for the engraftment. The appellant referred to documents D49, D47 and D43 which showed that it was common sense to wait until the antibody was substantially cleared before HSC transplantation. These documents, however, relate to cytotoxic agents and radioimmunotherapy, but not to antibodies interfering with cellular signalling. In view of the completely different mechanism involved the board considers the disclosure in these documents not relevant.

49. Even combining the disclosure in document D3 with that in document D1 would not have filled the gaps between the claimed subject-matter and the disclosure of

document D3. Document D1 teaches that antibody ACK2 did not deplete the more primitive stem cell subset (see page 68, lines 2 to 7) and thus used other antibodies in its *in vivo* experiments (e.g. 2B8). Document D1 also provides no information on the potential success of allogeneic or autologous engraftment when using the ACK2 antibody or on the required clearance of the antibody to less than 10 ng/ml (see point 29. above).

50. Thus, the skilled person starting from the disclosure in document D3 would not have arrived at the subject-matter of claim 1.

51. In view of the above considerations, the subject-matter claimed involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the main request with a description and drawings adapted thereto, as necessary.

The Registrar: The Chair:

I. Aperribay A. Chakravarty

Decision electronically authenticated