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Datasheet for the decision of 7 December 2023

Case Number: T 1514/20 - 3.3.08

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Title of invention:
Reprogramming T cells and hematopoietic cells

Patent Proprietor:
FUJIFILM Cellular Dynamics, Inc.

Opponents:
Strawman Limited
Lonza Walkersville, Inc. (opposition withdrawn)
Mathys & Squire LLP

Headword:
Reprogramming $CD34^+$ HPCs/FUJIFILM

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no) - reasonable expectation of success (yes)

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Case Number: T 1514/20 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 7 December 2023

Appellant I: (Opponent 1)	Strawman Limited Orchard Lea, Horns Lane, Combe, Whitney, Oxfordshire OX29 8NH (GB)
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Respondent: (Patent Proprietor)	FUJIFILM Cellular Dynamics, Inc. University Research Park 525 Science Drive, Suite 200 Madison, WI 53711 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 29 April 2020 concerning maintenance of the European Patent No. 2548950 in amended form**

Composition of the Board:

Chair T. Sommerfeld
Members: A. Schmitt
D. Rogers

Summary of Facts and Submissions

I. The appeals lodged by opponent 1 (appellant I) and opponent 3 (appellant II) lie from the opposition division's interlocutory decision that European patent No. 2 548 950 (the patent) as amended in the form of the main request filed by letter dated 2 December 2019 and received on 2 January 2020 and the invention to which it relates meet the requirements of the EPC.

II. The patent entitled "*Reprogramming T cells and hematopoietic cells*" was granted on the basis of European patent application No. 12 177 512.6.

III. Three oppositions were filed against the patent. The opposition proceedings were based on the grounds in Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and those in Article 100(b) and (c) EPC.

IV. On 31 July 2020, opponent 2 withdrew its opposition.

V. In reply to the appeals, as its main request, the patent proprietor (respondent) maintained the set of claims of the main request underlying the decision under appeal and submitted sets of claims of 47 auxiliary requests (auxiliary requests 1 to 24, 1a and 3a to 24a).

Claim 1 of the main request reads as follows:

"1. An *in vitro* method for producing induced pluripotent stem cells from human $CD34^+$ hematopoietic progenitor cells comprising the steps of:

(a) obtaining a cell population from a blood sample of peripheral blood comprising $CD34^+$ hematopoietic progenitor cells, wherein said blood sample is from a subject and wherein said blood sample was obtained without mobilizing the $CD34^+$ hematopoietic progenitor cells in the subject prior to obtaining the blood sample;
(b) enriching said cell population for $CD34^+$ hematopoietic progenitor cells; and
(c) producing iPS cells from the $CD34^+$ hematopoietic progenitor cells of the cell population to provide an iPS cell population, wherein producing iPS cells from the $CD34^+$ hematopoietic progenitor cells of the population comprises introducing reprogramming factors into the $CD34^+$ hematopoietic progenitor cells, and wherein the reprogramming factors are reprogramming proteins comprising a Sox family protein and an Oct family protein."

Claim 1 of each of the 47 auxiliary requests submitted with the reply to the appeal differs from claim 1 of the main request on account of one or more of the following features:

- step (a) reads as follows: "(a) obtaining a cell population from a blood sample of peripheral blood comprising $CD34^+$ hematopoietic progenitor cells, wherein said blood sample is from a subject whose cells have not been mobilized";

- the claim contains the disclaimer "and wherein the source of the cell population is not umbilical cord";

- the subject in step (a) is defined as "a subject whose cells have not been mobilized by extrinsically applied factors";

- the subject in step (a) is additionally defined as being "healthy";

- the reprogramming factors in step (c) are further defined.

Since each of these amendments were introduced to address objections concerning added matter, sufficiency of disclosure or novelty, but not to address the objections raised against claim 1 of the main request with respect to inventive step (see pages 145 to 153 of the reply to the appeals), the precise wording of claim 1 of each of the 47 auxiliary requests is not relevant for this decision.

VI. The board summoned the parties to oral proceedings in accordance with their requests and, in a communication pursuant to Article 15(1) RPBA, expressed its preliminary opinion, *inter alia*, that claim 1 of the main request and claim 1 of each of the 47 auxiliary requests did not involve an inventive step.

VII. Appellant I and the respondent were represented at the oral proceedings. Appellant II did not attend the oral proceedings, as announced in a submission dated 16 June 2023.

VIII. The following documents are referred to in this decision:

D1 Loh et al., Blood, 113(22), 2009, 5476-5479
D1a Supplemental materials for: Loh et al. (D1)
D2 Eminli et al., Nat Genet, 41(9), 2009, 968-976
D14 Tura et al., J Transl Med., 5, 2007, 37 (10 pages)

D22 Saito et al., Nature Protocols, 1(4), 2006, 2178-2183

D36 Pelus, Curr Opin Hematol., 15(4), 2008, 285-292

D41 Anderlini, Curr Opin Hematol., 16(1), 2009, 35-40

D64 Philpott et al., British Journal of Haematology, 97, 1997, 146-152

D66 Bender et al., Clinical Immunology and Immunopathology, 70(1), 1994, 10-18

D68 Cottier-Fox et al., ASH Education Book, 1, 2003, 419-437

IX. The appellants' arguments, insofar as they are relevant to the decision, are summarised as follows.

Main request
Inventive step (Article 56 EPC) - claim 1

The claimed method was not inventive in view of the method disclosed in document D1 and/or that disclosed in document D2. The only difference between the claimed method and these methods was the source of the human $CD34^+$ hematopoietic progenitor cells ($CD34^+$ HPCs), which were obtained from "non-mobilised" peripheral blood instead of "mobilised" peripheral blood (D1) or cord blood (D2). No evidence was on file that the induced pluripotent stem cells (iPS cells) produced by the claimed method differed from those produced by the methods in documents D1 and D2.

The claimed method avoided the risks to the blood donors associated with granulocyte colony-stimulating factor (G-CSF) treatment and overcame the limited availability of cord blood. The technical effect of this difference was an improved source of the $CD34^+$ HPCs and the objective technical problem was that of

providing an improved source of $CD34^+$ HPCs for use in a method for producing iPS cells from human $CD34^+$ HPCs.

For solving this problem, the use of non-mobilised blood as a source of $CD34^+$ HPCs was obvious to the skilled person since it was known to contain $CD34^+$ HPCs (e.g. D14, D22 and D64), was not associated with any health risks for the donor and was readily available in large volumes. The number of $CD34^+$ HPCs present in non-mobilised blood was sufficient to achieve reprogramming that required about 5×10^4 CD34+ HPCs (third paragraph of D1a). $CD34^+$ HPCs could be isolated and enriched from non-mobilised blood by known methods (e.g. D1 and D22).

The respondent did not provide any evidence that any of the alleged biological differences in $CD34^+$ HPCs from mobilised and non-mobilised blood (D14, D41 and D66) would have had an effect on the reprogramming efficiency of these cells. Documents D1 and D2 disclosed the proof of principle that $CD34^+$ HPCs could be reprogrammed. Since each $CD34^+$ HPC subtype was an immature cell (first paragraph of introduction of D66), the skilled person would have considered that each $CD34^+$ subtype could be reprogrammed. The claim did not require the HPCs to be $CD34^+/CD38^-$ HPCs.

The decrease in $CD34^+/CD38^-$ HPCs during cell culture observed in document D1 was irrelevant since it was correlated in document D1 with the expansion capacity of the cells, but not with reprogramming efficiency (right-hand column on page 5476 of D1 and Figure S1C in D1a). Evidence from transplantation experiments, in which a much higher quantity of starting material was required (e.g. D68), had no bearing on the reprogramming of cells, which could multiply in an unlimited manner once they had been reprogrammed.

Document D2 also supported the fact that any $CD34^+$ HPC subtype could be reprogrammed, since it taught that, while any immature cell population could be more efficiently reprogrammed than terminally differentiated cells (page 973, right-hand column, last sentence of first full paragraph), within immature cell populations there was no strict correlation between differentiation stage and reprogramming efficiency (page 975, left-hand column, third paragraph). The conclusions drawn in this part of document D2 were provided as general statements. It was not relevant that the experiments had been conducted with mouse cells.

In its last paragraph on page 975, document D2 did not provide teaching leading away from other sources for suitable progenitor cells, as it referred to cord blood cells only as an example source and, in general, suggested using somatic progenitor cells for reprogramming.

Hence, neither the different quantity nor an alleged difference in quality of the $CD34^+$ HPCs from non-mobilised blood compared with those from cord blood or mobilised blood would have discouraged the skilled person from using non-mobilised blood as a source of $CD34^+$ HPCs for reprogramming.

Auxiliary requests 1 to 24, 1a and 3a to 24a
Inventive step (Article 56 EPC) - claim 1

The claimed method in each of the auxiliary requests was not inventive for the same reasons as the method in claim 1 of the main request.

X. The respondent's arguments, insofar as they are relevant to the decision, are summarised as follows.

Main request
Inventive step (Article 56 EPC) - claim 1

The difference between the claimed method and the method disclosed in document D1 was the blood source of the $CD34^+$ HPCs. The objective technical problem was to provide an improved method for producing iPS cells. The improvement involved avoiding detrimental effects due to the use of G-CSF for obtaining mobilised blood and easier accessibility of the blood sample that made the reprogramming method more convenient and safer.

It was not obvious to the skilled person to use non-mobilised peripheral blood to solve this problem since the prior art lacked a pointer to this. Mobilisation of blood by G-CSF was the gold standard in therapeutic applications and the primary source of HPCs (page 2 of D36). The skilled person did not have any incentive to modify the teaching in document D1 in this respect. Moreover, the skilled person would not have expected that $CD34^+$ HPCs from non-mobilised blood could be reprogrammed to iPS cells in an efficient manner in view of the different quantity and quality of $CD34^+$ HPCs present in non-mobilised peripheral blood compared with mobilised blood and cord blood.

It was clear from the disclosure in documents D1 and D2, which used blood sources comprising a high quantity of $CD34^+$ HPCs, that a large amount of these cells was required to achieve reprogramming. This was confirmed in Example 11 of the patent, in which $CD34^+$ HPCs had been isolated from 8 litres of blood and the reprogramming efficiency was only approximately

10 colonies per 100 000 cells (last sentence of paragraph [0364] of the patent). Document D1 disclosed that $CD34^+$ HPCs could not be expanded by culturing (right-hand column on page 5476 of D1). The skilled person hence would not have expected that a sufficient number of $CD34^+$ HPCs could be obtained from non-mobilised peripheral blood for reprogramming. The disclosure in document D22 was not relevant in this context as it did not relate to the reprogramming of cells.

$CD34^+$ HPCs from non-mobilised peripheral blood were biologically distinct from those present in cord blood and mobilised peripheral blood in terms of various parameters including subtype and number (Figure 4 of D66; page 4, left-hand column, second paragraph of D14), chromosomal and gene expression alterations (pages 5 and 6 of D41), and proportion of apoptotic cells (page 146, right-hand column, second paragraph of D64). Each of these differences was expected to affect reprogramming.

In particular, each $CD34^+$ subtype was not expected to be equally amenable to reprogramming. Document D66 demonstrated that the multipotential $CD34^+/CD38^-$ HPCs were barely present at all in non-mobilised blood (Figure 4), a fact that would have discouraged the skilled person from using non-mobilised blood. Document D1 disclosed that the number of $CD34^+/CD38^-$ HPCs decreased rapidly in culture and that the viral transduction therefore had to be performed soon (right-hand column on page 5476 of D1 and Figure S1C of D1a). This demonstrated that $CD34^+/CD38^-$ HPCs were the desirable cells. The patent also mentioned the importance of this particular subtype of $CD34^+$ HPCs (paragraphs [0037] and [0044] of the patent).

Document D2 confirmed that the differentiation stage had a strong impact on reprogramming efficiency and kinetics and that immature cell populations gave rise to iPS cells at higher efficiency (first full sentence in the right-hand column on page 969, last sentence of first full paragraph in right-hand column on page 973).

Documents D1 and D2 hence taught the skilled person which blood sources must be used to obtain a sufficient number of suitable $CD34^+$ HPCs. Document D2 additionally referred to cord blood as a safer source of iPS cells and hence provided teaching leading away from using other blood sources (last sentence on page 975). The experiments disclosed in document D2 with tissue-derived mouse hematopoietic cells were not relevant for human blood cells. Based on the teaching in documents D1 and D2 and the scarce number of suitable $CD34^+$ HPCs present in non-mobilised blood, the skilled person would not have used it as a source of cells for reprogramming $CD34^+$ HPCs. The fact that non-mobilised human blood did contain sufficient numbers of $CD34^+$ HPCs that were amenable to reprogramming was unexpected.

Auxiliary requests 1 to 24, 1a and 3a to 24a
Inventive step (Article 56 EPC) - claim 1

The respondent did not submit any arguments relating to inventive step that were specific to any of the auxiliary requests.

XI. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

XII. The respondent requested that the appeals be dismissed (main request, the patent as maintained by the opposition division) or, alternatively, that the patent be maintained on the basis of one of the 47 auxiliary requests submitted with the reply to the appeals.

Reasons for the Decision

Appellant not represented at the oral proceedings

1. As announced in writing, appellant II was not represented at the oral proceedings (see section VII. above). In accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the oral proceedings were continued in the absence of appellant II, which was considered to be relying only on its written case.

Main request
Inventive step (Article 56 EPC) - claim 1

2. The claim concerns a method for producing induced pluripotent stem cells (iPS cells) from human $CD34^+$ hematopoietic progenitor cells (HPCs) wherein the $CD34^+$ HPCs originate from a peripheral blood sample that was obtained "without mobilizing the $CD34^+$ hematopoietic progenitor cells in the subject prior to obtaining the blood sample" (see section V. for the full wording of the claim).

3. For the assessment of inventive step, the expression "mobilizing the $CD34^+$ hematopoietic progenitor cells in the subject prior to obtaining the blood sample" is interpreted, as proposed by the respondent, as referring to the recruitment of $CD34^+$ HPCs from the bone marrow into a subject's blood by administering

extrinsic factor(s), such as e.g. granulocyte colony-stimulating factor (G-CSF), to the subject. A blood sample or $CD34^+$ HPCs from a subject which has been treated in this manner are hereinafter designated as the "mobilised blood sample" or "mobilised $CD34^+$ HPCs", while a blood sample or $CD34^+$ HPCs from a subject which has not been treated in this manner are designated as the "non-mobilised blood sample" or "non-mobilised $CD34^+$ HPCs".

Closest prior art, difference and objective technical problem

4. In the decision under appeal, document D1 was considered the most appropriate starting point for the assessment of inventive step, a view that was shared by the respondent. Document Dl discloses a method of producing iPS cells from human $CD34^+$ HPCs by introducing the reprogramming factors OCT4, SOX2, KLF4 and MYC into $CD34^+$ HPCs. The $CD34^+$ HPCs were isolated from a blood sample from a donor that had been treated with G-CSF to mobilise HPCs from the bone marrow into the blood, i.e. from a mobilised blood sample.

5. The parties agreed that the claimed method differs from that disclosed in document D1 only on account of the source of the blood sample from which the $CD34^+$ HPCs were obtained. In the claimed method, a non-mobilised blood sample is used (see point 2. above), and accordingly, in contrast to the teaching in document D1, the HPCs were not mobilised from the bone marrow into the blood by G-CSF or any other extrinsic factor.

6. The respondent identified two technical effects of this difference, namely increased safety and increased convenience. Indeed, non-mobilised blood, which can be

acquired from any healthy donor and from blood banks, is more easily accessible than G-CSF-mobilised blood, which can only be obtained after the donor has been repeatedly treated with G-CSF (see e.g. the third paragraph on page 1 of D1a), a procedure that is associated with certain risks to the donor (see e.g. first full paragraph on page 2 of D36). The technical effects of the difference as defined by the respondent are therefore correct and constitute improvements.

7. However, there is no evidence of any difference between iPS cells obtained by the method in document D1 and iPS cells obtained by the claimed method. It is hence not the method of producing iPS cells *per se* that is improved, but the accessibility of the blood source and the safety of the donor. The objective technical problem can therefore be formulated as that of providing a more convenient and safer method for producing pluripotent stem cells from human $CD34^+$ HPCs.

Obviousness

8. In a first line of argument, the respondent considered that, since G-CSF treatment was the "gold" standard for HPC mobilisation (see the heading on page 2 of D36), the skilled person had no incentive to modify the protocol in document D1; however, this line of argument is not persuasive since document D36 refers to G-CSF treatment as the "gold" standard in the context of hematopoietic transplantation, in which the mobilised HPCs must directly engraft and which therefore requires a very high number of $CD34^+$ HPCs (2×10^6 cells/kg; see first full paragraph on page 2 of D36 and abstract of D68). This is different from the production of iPS cells, in which a single $CD34^+$ HPC that could be reprogrammed would be sufficient to fulfil this purpose

and in which, as disclosed in document D1, only 5×10^4 $CD34^+$ HPCs were required to produce 5 to 10 iPS cells (see last full sentence in the left-hand column on page 5477). The fact that G-CSF mobilisation was the "gold" standard for obtaining sufficient $CD34^+$ HPCs for transplantation is therefore irrelevant for the claimed method.

9. Moreover, the disadvantages associated with G-CSF mobilisation in terms of safety and accessibility were known to the skilled person (see point 6. above). In order to improve the method in document D1 with respect to these disadvantages (see point 7. above), the skilled person would have considered other sources of $CD34^+$ HPCs. $CD34^+$ HPCs are only present in a few other sample types including bone marrow, umbilical cord blood, blood mobilised by factors other than G-CSF and, to a lesser extent, non-mobilised peripheral blood (see e.g. Figure 1(a) of D14 and Figure 4 of D66).

10. Of these possible sources for $CD34^+$ HPCs, non-mobilised peripheral blood is easily accessible and is safer for the donor, since no treatment with a mobilising agent is necessary. Bone marrow is neither easily accessible nor safer to obtain, and umbilical cord blood is only available shortly after birth and is rare. Blood mobilised by any factors other than G-CSF suffers from similar deficiencies in terms of accessibility and safety as G-CSF-mobilised blood since donors also have to undergo treatment with a mobilising agent before the blood can be collected.

11. Non-mobilised peripheral blood is therefore the only known source of $CD34^+$ HPCs that is both more easily accessible and safer for the donor than G-CSF-mobilised peripheral blood.

12. It was also already known to the skilled person that $CD34^+$ HPCs could be isolated from non-mobilised blood by e.g. magnetic cell sorting (see e.g. D22: abstract; lines 9 to 11 of the right-hand column on page 2178; section 17 on page 2180). For this teaching, it is irrelevant that document D22 is concerned with culturing of human mast cells and not with reprogramming HPCs. Document D22 demonstrates that it was commonly known that $CD34^+$ HPCs were contained in non-mobilised blood and could be purified from it, albeit in lower numbers than from G-CSF mobilised blood. This is also confirmed in documents D14 (Figure 1(a), *supra*) and D64 (first full paragraph of the right-hand column on page 146).

13. In view of these known properties of non-mobilised blood, the skilled person would have taken it into account as a possible source of $CD34^+$ HPC to solve the objective technical problem. Therefore, contrary to the appellant's assertion, no specific pointer to non-mobilised blood was necessary in document D1. The inventive step of the claimed method hinges on the question of whether the skilled person would have reasonably expected that iPS cells could be produced from human $CD34^+$ HPCs obtained from non-mobilised peripheral blood.

14. In addition to the reprogramming of mobilised human $CD34^+$ HPCs, the prior art also discloses the reprogramming of $CD34^+$ HPCs from human umbilical cord blood (see second full paragraph in the right-hand column on page 973 of D2). As paraphrased in both D1 and D2, both documents hence disclose the "proof of principle" that human hematopoietic progenitor cells can be reprogrammed into iPS cells with the same four

reprogramming factors used in the prior art for many other cell types (see the last full sentence in the right-hand column on page 5478 of D1 and the last sentence of the second full paragraph in the right-hand column on page 973 of D2).

15. The skilled person therefore knew from two different documents that human $CD34^+$ HPCs could be reprogrammed into iPS cells by the same prior-art technique and would therefore have expected that human $CD34^+$ HPCs from any source, including non-mobilised peripheral blood, could be reprogrammed into iPS cells.

16. The respondent asserted that, in view of the low number of $CD34^+$ HPCs present in non-mobilised peripheral blood, the low reprogramming success rate observed in document D1 and the fact that expansion of $CD34^+$ HPCs by cultivation was not possible, the skilled person would not have expected that non-mobilised blood contained sufficient $CD34^+$ HPCs for successful reprogramming.

17. However, methods for isolating and enriching $CD34^+$ HPCs from human blood were known in the art (see e.g. document D22, *supra;* see also third paragraph of D1a). Therefore, the relatively low number of $CD34^+$ HPCs in non-mobilised blood could easily be compensated for by using a higher blood volume as the starting material in order to collect a sufficient number of $CD34^+$ HPCs (about 5×10^4 cells; see third paragraph of D1a). No arguments were provided by the respondent that this number of $CD34^+$ HPCs could not be collected from non-mobilised blood samples using any of these prior-art techniques. The relatively low number of $CD34^+$ HPCs in non-mobilised blood was therefore, as such, not a reason for the skilled person to disregard peripheral

blood as a sample source of $CD34^+$ HPCs for producing iPS cells.

18. The respondent also argued that the skilled person was dissuaded from using non-mobilised peripheral blood as a source of $CD34^+$ HPCs for producing iPS cells since $CD34^+$ HPCs from non-mobilised blood were biologically distinct from $CD34^+$ HPCs in G-CSF mobilised and cord blood. The respondent referred in particular to the very low, almost non-existent number of $CD34^+/CD38^-$ multi-potential HPCs in non-mobilised peripheral blood (Figure 4 of D66) and the fact that the differentiation stage of a cell had an impact on the efficiency of reprogramming (see e.g. the first sentence of the right-hand column on page 969 of D2).

19. This line of argument is not persuasive either, however. The CD34 antigen is a stage-specific marker that identifies cells in the earliest stages of hematopoietic differentiation (see first paragraph of the right-hand column on page 10 of D66). Any cell expressing CD34 is therefore a relatively immature HPC. In line with this knowledge, documents Dl and D2 teach the use of the entire population of $CD34^+$ HPCs for the introduction of reprogramming factors and neither of these documents discloses that the $CD34^+$ HPCs should comprise or lack any other cell surface marker or that only $CD34^+/CD38^-$ multi-potential HPCs could be reprogrammed (see the third paragraph of D1a, the supplemental materials in D1; see second full paragraph of the right-hand column on page 973 of D2).

20. Document D1 reports a progressive decrease in $CD34^+/CD38^-$ HPCs and increase in differentiated cells during cell culture that correlates with the expansion capacity of the HPCs (right-hand column on page 5476

of D1 and supplementary Figure S1C in D1a). The conclusion from this observation is that the viral transduction (with the reprogramming factors) should be performed sufficiently early, "*when the majority of the cells were still expressing CD34*" (D1, *ibid.*). Hence, also in this passage, document D1 points to CD34 as the decisive marker. This passage therefore would not have discouraged the skilled person from using $CD34^+$ HPCs from non-mobilised blood for reprogramming.

21. Document D2 discloses that in hematopoietic mouse cells isolated from the thymus, spleen or bone marrow, immature cell populations could be more efficiently reprogrammed than terminally differentiated cells (page 973, right-hand column, last sentence of the first full paragraph); however, the reprogramming efficiency did not correlate with the proliferation rate (paragraph bridging pages 973 and 974), and, within immature cell populations, did not correlate with the differentiation stage (page 975, left-hand column, third paragraph). Since CD34 is a marker for immature cells (see point 19. above), the disclosure in document D2 also does not support the respondent's allegation that $CD34^+/CD38^-$ HPCs would necessarily be more efficiently reprogrammed as they were more immature. Instead, despite being obtained from mouse hematopoietic cells, the data in document D2 points to the contrary.

22. The fact that the patent also mentions $CD34^+/CD38^-$ HPCs (in paragraphs [0037] and [0044]) is not relevant, either. This subtype of $CD34^+$ HPCs is not recited in the claims and is disclosed in paragraphs [0037] and [0044] merely as one of several cellular subtypes included within the "*primitive hematopoietic cells types or precursor cells*" that all may be converted

into iPS cells (see in particular the last sentence of paragraph [0044] of the patent).

23. In its last paragraph on page 975, document D2 discusses that progenitor cells "*such as cord blood cells are likely to have accrued few, if any, genetic aberrations compared with differentiated cell types and may thus be a safer source for iPS cells*". This section does not provide teaching leading away from sources other than cord blood for suitable progenitor cells, as argued by the respondent, since it refers to cord blood cells only as an exemplary source ("such as") for these progenitor cells. This is also evident from the preceding sentence in the same section of document D2, which specifically refers to somatic progenitor cells "*from adult tissues*" and explicitly states that the use of said cells "*should make the derivation of patient-specific iPS cell lines more efficient and thus affordable*".

24. In view of the above considerations, the knowledge of varying percentages of specific $CD34^+$ HPC subtypes, including $CD34^+/CD38^-$ HPCs, in umbilical cord blood, mobilised and non-mobilised peripheral blood was no reason for the skilled person to expect that iPS cells could not be produced from $CD34^+$ HPCs isolated from non-mobilised peripheral blood.

25. The respondent also pointed out that chromosomal and gene expression alterations (pages 5 and 6 of D41) and a different proportion of apoptotic cells (last paragraph of the Summary on page 146 of D64) were found in $CD34^+$ HPCs from G-CSF mobilised blood compared with $CD34^+$ HPCs from non-mobilised blood; however, the respondent has not submitted any evidence or convincing arguments for why the skilled person would have

considered that any of these biological differences would have had an effect on the reprogramming of $CD34^+$ HPCs to such an extent that no successful reprogramming of $CD34^+$ HPCs from non-mobilised human blood could be expected. The respondent's conclusion that mobilised peripheral blood cells or cord cells were more amenable to being reprogrammed to iPS cells based on these differences is therefore only speculative, and not persuasive.

26. In summary, the respondent's arguments that different numbers of $CD34^+$ HPC subtypes and other biological differences observed between $CD34^+$ HPCs from umbilical cord blood, mobilised and non-mobilised peripheral blood would have led the skilled person to expect that iPS cells could not be produced from $CD34^+$ HPCs isolated from non-mobilised peripheral blood are not persuasive.

27. The claimed method hence does not involve an inventive step (Article 56 EPC).

Auxiliary requests 1 to 24, 1a and 3a to 24a
Inventive step (Article 56 EPC) - claim 1

28. The respondent has not submitted any arguments relating to inventive step that are specific to any of the auxiliary requests on file. The subject-matter of claim 1 of each of auxiliary requests 1 to 24, 1a and 3a to 24a does not involve an inventive step for the same reasons as the subject-matter of claim 1 of the main request (see points 4. to 27. above).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated