Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 25 March 2026

Case Number: T 0401/24 - 3.3.08

Application Number: 13869259.5

Publication Number: 2938724

IPC: C12N5/071, C12N5/0735, G01N33/50

Language of the proceedings: EN

Title of invention:
Culturing of human embryonic stem cells at the air-liquid interface for differentiation into pancreatic endocrine cells

Patent Proprietor:
Janssen Biotech, Inc.

Opponent:
Zwicker Schnappauf & Partner
Patentanwälte PartG mbB

Headword:
Culturing of human embryonic stem cells/JANSSEN BIOTECH

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
Main request and auxiliary requests 4, 6, 8, 10, 12, 14 and 15 - added subject-matter - (yes)
Auxiliary requests 2 and 13 - Inventive step - (no)

Decisions cited:
G 0002/10, T 0997/06, T 0056/08, T 1634/13, T 1173/17

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 0401/24 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 25 March 2026

Appellant: (Opponent)	Zwicker Schnappauf & Partner Patentanwälte PartG mbB Hansastr. 32 80686 München (DE)
Representative:	Gaentzsch, Peer Christian and Kur, Esther Zwicker Schnappauf & Partner Patentanwälte Part mbB Hansastraße 32 80686 München (DE)
Respondent: (Patent Proprietor)	Janssen Biotech, Inc. 800/850 Ridgeview Drive Horsham, PA 19044 (US)
Representative:	Sentner, Ulrich, Schwendemann, Alexander and Hastreiter, Simon 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/ electronically transmitted on 1 February 2024 concerning maintenance of the European Patent No. 2938724 in amended form**

Composition of the Board:

Chair	T. Sommerfeld
Members:	M. Montrone
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2 938 724 B1 ("the patent") was granted for European patent application No. 13 869 259.5 which has been filed as International patent application published as WO 2014/105543 (the "patent application").

II. An opposition was filed against the granted patent. The patent was opposed on the grounds for opposition under Article 100(a) EPC in conjunction with Articles 54 and 56 EPC, Article 100(b) EPC and Article 100(c) EPC.

III. The present appeal has been filed by the opponent ("appellant") against an interlocutory decision of an opposition division according to which the patent could be maintained in amended form on the basis of the claims of the main request filed on 10 October 2023. In support of their case, *inter alia* a new expert declaration (D31) was filed.

IV. In reply, the patent proprietor ("respondent") re-submitted the main request and submitted auxiliary requests 1 to 15 and a new expert declaration (D32).

V. In a communication pursuant to Article 15(1) RPBA, the board provided its preliminary assessment.

VI. In reply thereto both parties submitted further arguments.

VII. Oral proceedings were held in the presence of both parties during which the respondent withdrew auxiliary requests 1, 3, 5, 7, 9 and 11.

VIII. Claims 1 and 12 of the main request read:

"1. A method of producing human cells expressing markers characteristic of pancreatic endocrine cells comprising differentiating human cells expressing markers characteristic of pancreatic foregut precursor cells into human cells expressing markers characteristic of pancreatic endoderm cells while culturing at the air-liquid interface, and differentiating said human cells expressing markers characteristic of pancreatic endoderm cells into human cells expressing markers characteristic of pancreatic endocrine cells by treatment with at least one medium supplemented with an ALK5 inhibitor II and a thyroid hormone selected from triiodothyronine, thyroxine, GC1, 3,5-diiodothyropropionic acid, KB-141, MB07344, T0681, and GC-24 and mixtures thereof, while culturing at the air-liquid interface".

"12. An *in vitro* cell culture comprising a population of differentiated human cells expressing markers characteristic of pancreatic endocrine cells wherein

at least thirty percent of said differentiated cells are single hormone insulin positive cells expressing NKX6.1,

and wherein the population is obtained by a method according to any one of claims 1-3".

IX. Claim 12 of auxiliary request 2 differs from that of the main request in that the feature "*at least thirty percent*" has been replaced by "*>30%*".

X. Claim 12 of auxiliary request 4 differs from that of the main request in that the feature "*wherein the cell*

culture further comprises an ALK5 inhibitor II and a thyroid hormone selected from triiodothyronine, thyroxine, GC-1,3,5-diiodothyropropionic acid, KB-141, MB07344, T0681, and GC-24 and mixtures thereof;" has been added.

XI. Claim 12 of auxiliary request 6 differs from that of the main request in that the feature "*a method according to any one of claims 1-3*" has been replaced by "*a method according to Example 10*".

XII. Claim 12 of auxiliary request 8 combines the amendments of claims 12 of auxiliary requests 4 and 6.

XIII. Claim 12 of auxiliary request 10 differs from that of the main request in that the feature "*a method according to any one of claims 1-3*" has been replaced by "*a method consisting of the steps of:*
a) differentiating human pluripotent stem cells into cells expressing markers characteristic of pancreatic foregut precursor cells,
b) differentiating the human cells expressing markers characteristic of pancreatic foregut precursor cells into human cells expressing markers characteristic of pancreatic endoderm cells while culturing at the air-liquid interface, and
c) differentiating the human cells expressing markers characteristic of pancreatic endoderm cells into human cells expressing markers characteristic of pancreatic endocrine cells by treatment with at least one medium supplemented with an ALK5 inhibitor II and a thyroid hormone selected from triiodothyronine, thyroxine, GC-1, 3,5-diiodothyropropionic acid, KB-141, MB07344, T0681, and GC-24 and mixtures thereof, while culturing at the air-liquid interface".

XIV. Claim 1 of auxiliary request 12 differs from claim 1 of the main request in that the feature "*a method according to any one of claims 1-3*" has been replaced by "*a method of producing human cells expressing markers characteristic of pancreatic endocrine cells comprising differentiating human cells expressing markers characteristic of pancreatic foregut precursor cells into human cells expressing markers characteristic of pancreatic endoderm cells while culturing at the air-liquid interface, and differentiating said human cells expressing markers characteristic of pancreatic endoderm cells into human cells expressing markers characteristic of pancreatic endocrine cells by treatment with at least one medium supplemented with an ALK5 inhibitor II and a thyroid hormone selected from triiodothyronine, thyroxine, GC-1, 3,5-diiodothyropropionic acid, KB-141, MB07344, T0681, and GC-24 and mixtures thereof, while culturing at the air-liquid interface*".

XV. Claim 1 of auxiliary request 13 combines the amendments of claim 12 of auxiliary request 2 and of claim 1 of auxiliary request 12.

XVI. Claim 1 of auxiliary request 14 is identical to claim 12 of auxiliary request 10.

XVII. Claim 1 of auxiliary request 15 differs from that of auxiliary request 14 in that the feature "*at least thirty percen*t" has been replaced by "*>30%*".

XVIII. The following documents are mentioned in this decision:

D1: Cheng X. *et al.*, Cell Stem Cell, 2012, Vol. 10(4), 371-384

D10: Micallef S. J. *et al.*, Diabetologia, 2012, Vol. 55, 694-706

Annex E of D15: Sander M. *et al.*, Development, 2000, Vol. 127: 5533-5540.

XIX. The arguments of the parties relevant for the decision are dealt with in detail in the Reasons for the Decision.

XX. The relevant requests of the parties for the decision were the following (for the complete list of the parties' requests, see the minutes of the oral proceedings):

The appellant requested:
- that the decision under appeal be set aside and the patent be revoked;
- that auxiliary requests 2, 10 and 12 to 15 not be admitted into the appeal proceedings.

The respondent requested:
- that the appeal be dismissed and the patent be maintained on the basis of the main request, or, alternatively, on the basis of the claims of one of auxiliary requests 2, 4, 6, 8, 10 and 12 to 15 filed in reply to the appeal.

Reasons for the Decision

Main request

Claim construction - claim 12

1. Claim 12 is drafted as a product-by-process claim. The claimed subject-matter relates in essence to an *in*

vitro population of differentiated pancreatic human cells expressing markers characteristic of pancreatic endocrine cells ("stage 6 cells", patent, paragraph [0031]) obtained by the method of claims 1 to 3 and comprising at least 30% single hormone insulin positive cells expressing NKX6.1.

1.1 The term "*single hormone insulin positive cells*" in claim 12 according to its ordinary meaning indicates that these cells express one hormone only, i.e. insulin (patent, page 16, lines 1 and 2).

1.2 Further the molecule "*NKX6.1*" mentioned in claim 12 is a transcription factor (Annex E of D15, abstract and page 5533, right column, last paragraph) that is used as marker of pancreatic precursor cells and β cells (patent, page 5, lines 27 and 28). Mature β cells are naturally located in the pancreas of humans where they secrete insulin in a glucose-dependent manner.

1.3 Since the cells of claim 12 are not further specified in the cell culture except for co-expressing insulin and NKX6.1 and their presence at a minimum percentage (at least 30%), the board agrees with the appellant that claim 12 encompasses any *in vitro* cell population containing cells that co-express insulin and NKX6.1 irrespective of the amount in which these two proteins are expressed, e.g. at high or low levels.

1.4 It was contentious between the parties whether potential properties of the claimed cells observed after their *in vivo* transplantation limit the *in vitro* cell culture of claim 12.

1.5 According to the case law of the Boards of Appeal a process feature in a product-by-process claim

contributes to the novelty and inventiveness of such a claim only insofar as this feature gives rise to a distinct and identifiable characteristic of the product as such (here an *in vitro* cell population). A product-by-process claim, like any other product claim, has to be interpreted in an absolute sense, i.e. independently of the process (see Case Law of the Boards of Appeal of the EPO, 11th edition 2025 ("Case Law"), II.A.7.2).

1.6 The board agrees with the appellant that the cell culture of claim 12 being a product-by-process is not limited by an *in vivo* or a therapeutic use. Accordingly the respondent's argument is not convincing that the claimed cells are also characterised by their functional resemblance to mature β cells as observable twelve weeks after their transplantation into a host organism (Example 11 of the patent). It cannot be excluded that the *in vivo* environment acting on the transplanted cells causes a further cell maturation so that the cells acquire properties that are absent from the claimed *in vitro* cell culture.

Added subject-matter - claim 12

2. In the following, references to the application as filed are to the patent application (WO 2014/105543).

3. The opposition division held (decision under appeal, section 3.17) that the feature "*at least 30%*" in relation to single hormone pancreatic endocrine cells, was derivable from paragraph [0143] of the application as filed which disclosed that more than 30% of the cells obtained by the method of the invention were single hormone insulin positive and expressed NKX6.1, while claim 93 as filed disclosed the feature "*at least thirty percent*" of claim 12 in general.

4. The board does not agree that these passages can provide a basis for the feature under dispute.

5. Claim 93 as filed reads as follows: "*An in vitro cell culture comprising a population of differentiated pluripotent stem cells expressing markers characteristic of pancreatic endocrine cells wherein at least thirty percent of said differentiated cells express NKX6.1 and insulin*" (emphasis added). It is uncontested that this is the sole disclosure in the application as filed for the feature "*at least thirty percent*" mentioned in claim 12.

5.1 In comparing the claims, claim 93 as filed differs from claim 12 of the main request *inter alia* in that it does not mention the feature "*single hormone insulin positive cells*". Instead claim 93 as filed mentions that the cell culture comprises certain cells "*expressing markers characteristic of pancreatic endocrine cells*" (stage 6 cells) of which "*at least thirty percent...express NKX6.1 and insulin*".

5.2 Since claim 93 as filed is silent on the feature "*single hormone*" positive cells, this claim does not exclude that the cells defined therein express other hormones in addition to insulin. The ability of stage 6 cells to express more than one hormone is, for example, reported in Example 10 of the application as filed. Page 75, lines 10 to 12 of the application as filed states in this context that: "*the majority of hormone positive cells were single hormone insulin positive cells (34% single hormone insulin positive cells, 7% single hormone glucagon positive cells, and 8% poly hormone cells*", emphasis added). Paragraph [0059] of the application as filed discloses that stage 6 cells

produce several hormones: insulin, glucagon, somatostatin, ghrelin and pancreatic polypeptide. It is uncontested that the stage 6 cells reported in Example 10 of the application as filed have been generated by a method encompassed by claim 1 and that these cells express NKX6.1 too (e.g. paragraphs [0179] and [0194]).

5.3 The other passage indicated by the opposition division, e.g. paragraph [0143] of the application as filed, mentions "*>30%*", i.e. a range that excludes 30%. Thus this disclosure cannot serve as a basis for the feature "*at least thirty percent*" of claim 12 because the claimed feature encompasses 30%.

6. The respondent submitted that the feature "*at least 30%*" of claim 12 had a basis in the application as filed because the generation of single hormone positive stage 6 cells co-expressing insulin and NKX6.1 was indicated therein as preferred. This was *inter alia* derivable from paragraph [0136] of the application as filed which was directed at a "*method of producing single hormone insulin positive cells expressing NKX6.1 cells by culturing at the air-liquid interface ..., preferably Stages 5 and 6*" (emphasis added). Further, claim 93 as filed disclosing literally the feature "*at least 30%*" provided the general framework of present claim 12. This did not change by the disclosure of paragraph [0143] of the application as filed since the statement "*optionally >30%*" was shown in brackets which indicated its exemplary character as confirmed by the reference to Example 10 of the application as filed. In light of the application as filed as a whole it was thus evident, that the statement "*optionally >30%*" in paragraph [0143] was an example of the more generic "*at least 30%*" mentioned in claim 93 as filed.

6.1 This is not convincing either. While the board agrees with the respondent that the application as filed is directed at the generation of single hormone positive cells, for the reasons outlined above (point 5.2), claim 93 as filed is not limited thereto. As set out above, the application as filed discloses in Example 10 that stage 6 cells generated by a method of the invention are not exclusively single hormone insulin positive, but include a significant percentage of poly-hormonal cells that express in addition to insulin and NKX6.1 other hormones.

6.2 Furthermore, while it is uncontested that paragraphs [0136] and [0142] of the application as filed provide the basis for the product-by-process feature of claim 12, the same does not hold true for the "*at least 30%*" feature of claim 12. Paragraph [0143] solely mentions "*optionally >30%*", thereby excluding 30%. Moreover while "*optionally*" indicates that this value relates to an exemplary range, paragraph [0143] does not mention single hormonal positive cells, but "*insulin positive cells*" only. This is in line with Example 10 as mentioned in this paragraph too, because a significant percentage of stage 6 cells reported are poly-hormonal (points 5.2 and 6.1 above).

7. Since claim 12 comprises thus added subject-matter, the main request does not meet the requirements of Article 123(2) EPC.

Auxiliary request 2

8. As set out in section VI above, claim 12 of auxiliary request 2 has been limited compared to the main request in that the feature "*at least thirty percen*t" has been

replaced by "*>30%*", i.e. a one side open range that excludes 30%.

Added subject-matter - claim 12

9. It is uncontested that the subject-matter of claim 12 complies with the requirements of Article 123(2) EPC. The board agrees thereto.

Inventive step - claim 12

Closest prior art and technical problem

10. The appellant argued that various documents represented the closest prior art for the *in vitro* cell culture of claim 12, including document D1. In the following only this line of argument will be assessed under inventive step.

11. For the issue of inventive step it was common ground that the difference between the *in vitro* cell culture of claim 12 and that of document D1 resided in a higher proportion of single hormone insulin positive cells expressing NKX6.1.

12. The effects ascribable to this distinguishing feature were contentious between the parties. The appellant argued that the effect of this difference rested solely in the provision of a higher percentage of desired cells in the claimed *in vitro* cell culture. The respondent submitted that the claimed cell culture not only contained a higher percentage of desired cells, but that these cells were of a higher quality too because they resembled more closely mature functional β cells. This additional property was supported by the data in Example 11 of the patent demonstrating that

when stage 6 cells obtained by the method of the invention were transplanted into mice, the cells secreted an amount of insulin that was comparable to that of adult β cells already at twelve weeks post transplantation.

13. In agreement with the appellant, the board considers that the respondent's argument asserting a higher quality of the claimed cells is not persuasive.

13.1 The following is relevant. It is common ground that experimental data are not on file which directly compare under identical conditions either *in vitro* or *in vivo* the insulin secretion of cells obtained by the method of the invention with those of D1 obtained by the method described in this document.

13.2 When novelty of the claimed cell culture over document D1 was discussed with the parties, the board agreed with the respondent that properties of cells grown under *in vitro* conditions (such as in D1) do not necessarily resemble the properties of cells grown *in vivo* and *vice versa*. Nor are properties comparable between cells differentiated *in vitro* under different culture conditions, for example, the claimed cells versus those of D1. Since it is established jurisprudence that the same standard of evidence has to be applied for evaluating the disclosure of the prior art and the patent, properties of cells observed solely under *in vitro* conditions cannot be compared with cell properties determined under *in vivo* conditions only.

13.3 Document D1 (page 7, first paragraph and Figure 5F) discloses *in vitro* data that solely assess the glucose-dependent insulin secretion ("glucose responsiveness") of stage 6 cells (generated by a method that differs

from that of the patent) compared to human primary islet cells containing mature β cells as positive control. It is common ground that the method by which pancreatic endocrine cells (stage 6 cells) are generated from progenitor cells fundamentally affects their properties, including glucose responsiveness. The observed *in vitro* glucose responsiveness of the cells generated in D1 can therefore not be extrapolated to the claimed stage 6 cells that have been generated by a different method.

13.4 The patent does not disclose any experimental data assessing *in vitro* the glucose responsiveness of the stage 6 cells obtained by the method of the invention. Nor are such *in vitro* data available from any other source. The patent reports in Example 11 (see also Figure 20) only that stage 6 cells obtained by the claimed method and being transplanted into mice secrete twelve weeks after transplantation insulin in amounts that are comparable to human islet cells. However, for the reasons indicated above (points 1.6 and 13.2) no conclusions can be drawn from these *in vivo* data in Example 11 and Figure 20 of the patent as regards the potential glucose responsiveness of these stage 6 cells when tested under *in vitro* conditions.

13.5 The respondent submitted that the available data on file nevertheless allowed an indirect comparison of the β cell resemblance between the claimed cell population and that of D1. While D1 disclosed that the cells obtained secreted insulin under *in vitro* conditions to an extent of "*~20% of the secretion of adult islet β cells*" (page 7, first paragraph), the cells of the claimed cell culture secreted insulin under *in vivo* conditions twelve weeks after their transplantation in amounts comparable to those of adult human islet cells

(Example 11 of the patent and Figure 20). This difference in insulin secretion suggested the superiority of the cells obtained by the method of the invention.

13.6 This is not convincing either. As set out above under claim construction (point 1.6), the increased insulin secretion of the transplanted cells in Example 11 of the patent could be due to a further maturation of the cells which may acquire new properties.

13.7 Therefore in the absence of data that directly compare the glucose responsiveness of the claimed cells vis-à-vis the cells of D1 either *in vitro* or *in vivo*, no conclusions can be drawn from the available data as regards their β cell resemblance.

14. In light of the considerations above, the sole technical effect ascribable to the distinguishing feature remains in the provision of a cell culture with a higher percentage of desired cells, i.e. of mono-hormonal cells that co-express insulin and NKX6.1. Consequently, the technical problem to be solved resides in the provision of an improved cell culture (because the claimed cell culture contains a higher percentage of desired cells).

15. In view of the experimental data disclosed in Example 10 of the patent, the board is satisfied that the *in vitro* culture of claim 1 solves this technical problem.

Obviousness

16. It remains to be assessed whether the skilled person starting from document D1 and faced with the problem identified above would have arrived at a cell culture

comprising a cell population as defined in claim 12 in an obvious manner.

17. The *in vitro* cell culture of claim 12 does not specify an absolute number of mono-hormonal stage 6 cells co-expressing insulin and NKX6.1, but a value ("*>30%*") which specifies a minimum percentage of these cells relative to the other cells present in the culture. This percentage of stage 6 cells is higher than that reported in D1 because D1 does not disclose which percentage of the 32% single insulin expressing clone 2 cells shown in Figure 5B co-express NKX6.1 too.

18. As regards NKX6.1, D1 discloses that the single insulin expressing cells of Figure 5B were cultured for 6 more days followed by a quantitative PCR for analysing the gene expression of insulin and various other markers that are commonly known to be involved in the differentiation of functional β cells (Figure 5C, legend). Page 6, second paragraph of D1 summarises this gene expression data by stating that "*Consistent with pancreatic differentiation, expression of PDX1, NKX6-1, and NEUROD1 were strongly induced (Figures 5C and S5C), while the expression of the EP cell marker SOX17 declined (Figure S5C)*" (emphasis added). Moreover as regards β cell differentiation, i.e. of single hormone insulin secreting cells in the pancreas, D1 states that "*If the same correction for INS expression is used, then both MAFA and NKX6-1 may be expressed in EP cell-derived c-peptide+ cells at comparable levels to those in adult β-cells*" (emphasis added, "*INS*" means insulin).

19. It is uncontested that it belongs to the common general knowledge at the filing date of the patent that single insulin positive β cells *in vivo* co-express NKX6.1.

Moreover D1 already suggests (point 18 above) that the single insulin positive cells obtained *in vitro* express the gene encoding NKX6.1 too. Although the exact percentage of cells co-expressing insulin and NKX6.1 proteins is unknown, D1 suggests that the NKX6.1 gene expression resembles that of adult β cells. Therefore the skilled person in seek of an improved cell population that contains a higher percentage of cells co-expressing insulin and NKX6.1 had a high expectation of success in arriving at this goal by enriching the cells of D1 further to a percentage approaching 100%.

20. Methods for enriching insulin positive cells were commonly known in the art, for example, by using the green fluorescent protein ("GFP") as marker (document D10, abstract). Therefore the skilled person by combining the cells of document D1 with the teaching of D10 would have arrived at the claimed *in vitro* cell culture in an obvious manner.

21. The respondent submitted that the cell differentiation protocols in documents D1 and D10 were different from each other and moreover differed from the one used in the patent. Accordingly the skilled person would not have relied on the teaching of D10.

22. The board does not agree. While it is true that documents D1 and D10 disclose different protocols for generating stage 6 cells, this difference is irrelevant for the issue at stake since the use of GFP as selection marker for enriching insulin secreting cells is not technically tied to a specific cell differentiating protocol. Thus, GFP as marker can be freely applied to any other protocol, such as that of D1 for enriching insulin secreting cells.

23. The respondent argued further that the skilled person would not have used a GFP labelling of stage 6 cells for enriching insulin secreting cells because this required GFP's insertion into the gene encoding insulin. Since cells had two gene copies of insulin only, the deletion of one of them by the insertion of GFP would have reduced the overall amount of insulin secreted from these cells.

24. This is not convincing either. As set out above under claim construction (point 1.3), the cells co-expressing insulin and NKX6.1 in the claimed cell culture are not specified by a particular amount of secreted insulin. It suffices that these cells co-express insulin and NKX6.1, irrespective of the insulin amount secreted.

25. Consequently, auxiliary request 2 lacks an inventive step (Article 56 EPC).

Auxiliary requests 4, 6, 8, 10, 12 and 14

26. As indicated in sections VII to X above, the subject-matter of claim 12 of auxiliary requests 4, 6, 8 and 10 contains the feature "*at least 30%*" single hormone insulin positive cells expressing NKX6.1.

27. The same applies to the subject-matter of claim 1 of auxiliary requests 12 and 14 (sections XI and XIII above).

Added subject-matter

28. Since claim 12 of auxiliary requests 4, 6, 8 and 10 and claim 1 of auxiliary requests 12 and 14 contain the feature "*at least 30%*", these claims comprise added

subject-matter for the same reasons set out above for claim 12 of the main request.

29. Consequently, auxiliary requests 4, 6, 8, 10, 12 and 14 contravene the requirements of Article 123(2) EPC for reasons analogous to those for claim 12 of the main request.

Auxiliary request 13

30. As indicated in section XII above, claim 1 of auxiliary request 13 combines the features of claim 12 of auxiliary request 2 with those of claim 1 of auxiliary request 12. Hence, claim 1 of auxiliary request 13 just differs from claim 1 of auxiliary request 12 in that the feature "*at least thirty percent*" has been replaced by "*>30%*". As such, this claim complies with Article 123(2) EPC.

Inventive step

31. The respondent has not made any submissions as to why this amendment which merely removes from the claimed scope one single percentage value, namely 30%, would render the claim inventive. Accordingly the reasons set out above under lack of inventive step for claim 12 of auxiliary request 2 apply likewise to the subject-matter of claim 1 of auxiliary request 13 (Article 56 EPC).

Auxiliary request 15

32. As set out above under sections XIII and XIV, claim 1 of auxiliary request 15 differs *inter alia* from the subject-matter of claim 12 of the main request in that:

- the claimed cell culture has been limited to a cell culture containing "*>30%*" of single hormone insulin positive cells co-expressing NKX6.1 and
- in that the claimed cell culture has been limited in that it is obtained by specified process steps due to the use of the "*consisting*" language.

Added subject-matter - claim 1

33. It is established case law that for the assessment of any amendment in a claim under Article 123(2) EPC the "gold standard" (G 2/10, OJ 2012, 376) applies which requires that any amendment can be made only within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the application as filed.

34. It was contentious between the parties whether the restriction of process steps a) to c) to the "*consisting*" language in claim 1 (for which the application as filed contains no explicit basis) comprises added subject-matter.

35. In a first line of argument, the respondent submitted that the term "comprising" always included the term "consisting" as a limiting case and that therefore a replacement of "comprising" by "consisting" did not add subject-matter according to the case law (e.g. T 997/06, Reason 29).

36. The board agrees with the appellant that the case law relied on by the respondent has been refined meanwhile so that it is now established case law that no general rule exists that the term "*comprising*" as such provides always, i.e. independent of the case at hand, a basis

for "*consisting of*". The older case law referred to by the respondent (e.g. T 997/06) is no longer followed by the Boards of Appeal (Case Law, II.E.1.15).

37. In a second line of argument, the respondent submitted that a cell culture obtained by a method that has been restricted to the specific process steps indicated in claim 1 was clearly envisaged in the application as filed due to the presence of pointers, in particular as derivable from the working examples (T 1173/17, Reason 5.4 and T 1634/13, Reasons 2.1 to 2.3). Furthermore the application as filed disclosed that the gist of the invention lied in the generation of stage 6 cells by a differentiation protocol which did not rely on further enrichment and/or purification steps. In support of their case, the respondent referred to paragraphs [0079], [0085] and in particular to Example 10 of the application as filed.

38. The board for the reasons submitted by the appellant does not agree.

38.1 A restriction of the method for obtaining the claimed *in vitro* cell culture to those steps explicitly indicated in claim 1 is not derivable from the application as filed. Contrary to the respondent's view, the application as filed uses consistently the "comprising" language for generating cells expressing markers being characteristic of pancreatic endocrine cells (stage 6 cells) (e.g. claim 1 as filed). It is established case law that a method using the "comprising" language for specifying its process steps encompasses more steps than solely those explicitly indicated (Case Law, II.E.1.15).

38.2 This is also evident from paragraph [0085] of the application as filed as referred to by the respondent which states as follows: "*In certain embodiments of the invention, to arrive at cells expressing markers characteristic of pancreatic endocrine cells, a protocol starting with pluripotent stem cells or inducible pluripotent cells, preferably pluripotent stem cells, is employed. This protocol includes the following:....*" (emphasis added).

38.3 The mentioning that the protocol "*includes*" certain process steps is not more restrictive than "comprises" because the general meaning of both verbs is identical (e.g. T 56/08, Reasons 2.5).

38.4 The respondent referred in addition to paragraph [0079] of the application as filed which reads as follows: "*As pluripotent cells differentiate towards β cells, they differentiate through various stages each of which may be characterized by the presence or absence of particular markers. Differentiation of the cells into these stages is achieved by the specific culturing conditions including the presence and lack of certain factors added to the culture media. In general, this differentiation may involve differentiation of pluripotent stem cells into definitive endoderm cells. These definitive endoderm cells may then be further differentiated into gut tube cells, which may, in turn, be differentiated into foregut endoderm cells. Foregut endoderm cells may be differentiated into pancreatic foregut precursor cells which can, in turn, be further differentiated into pancreatic endoderm cells, pancreatic endocrine precursor cells or both. These cells may then be differentiated into pancreatic hormone producing cells (such as β cells). This invention provides for staged differentiation of*

pluripotent stem cells toward pancreatic endocrine cells by culturing the cells at the air-liquid interface that exists within a culture vessel partially filled with medium, specifically by culturing Stage 4 to Stage 6 cells at the air-liquid interface".

38.5 The protocol mentioned in this paragraph is very generic and not limited to the specific process steps indicated in claim 1. Accordingly, from the disclosure of paragraph [0079] it cannot be directly and unambiguously derived that further process steps are excluded from this protocol.

39. Nor do the working examples of the application as filed lead to the conclusion that the claimed *in vitro* cell culture is obtained by a process that solely consists of the specific process steps indicated in claim 1.

39.1 Example 10 of the application as filed reports on a method for obtaining stage 6 cells. Also this method comprises more steps than the process steps indicated in claim 1. Paragraph [0193], for example, mentions that cells of a specific embryonic stem cell line were "*seeded as single cells*" in specific coated dishes in the presence of specific growth factors and inhibitors. The process steps of claim 1 are silent on any specific pluripotent cells, let alone a seeding step. Moreover Example 10 mentions specific growth conditions for generating stage 6 cells which are likewise missing from claim 1.

39.2 Since the process steps mentioned in Example 10 are more generic than those indicated in claim 1, pointers are lacking from Example 10 for using solely the claimed process steps. Such pointers are also not derivable from the other working examples of the

application as filed. Nor has a substantiation in this regard been submitted by the respondent.

40. It follows from the above that in the case at hand not only claim 1 as filed uses the term "comprising" for a process generating the cells comprised in the *in vitro* cell culture defined in claim 1 but also the general description including the working examples of the application as filed. Thus an *in vitro* cell culture comprising cells obtained by a process that consists solely of the process steps defined in claim 1 is neither disclosed in the application as filed nor clearly envisaged. The case at hand is thus similar to T 1173/17, Reason 5.4 which likewise held that the claimed invention comprised added subject-matter. While the case at hand differs from the situation dealt with in decision T 1634/13 since there the claimed "consisting of" embodiment was disclosed in the application as filed (Reasons 2.2).

41. Consequently the limitation of the process steps in claim 1 to the "consisting" language is not directly and unambiguously derivable from the application as filed. Claim 1 comprises thus added subject-matter and hence auxiliary request 15 contravenes the requirements of Article 123(2) EPC.

Admittance of auxiliary requests 2, 10 and 12 to 15 into the appeal proceedings

42. In view of the board's finding above that none of auxiliary requests 2, 10 and 12 to 15 is either inventive (Article 56 EPC: auxiliary requests 2 and 13) or comprises added subject-matter (Article 123(2) EPC: auxiliary requests 10, 12, 14 and 15), no purpose is

served in discussing the admittance of these auxiliary requests into the appeal proceedings.

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:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated