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Datasheet for the decision of 4 September 2024

Case Number: T 1553/22 - 3.3.04

Application Number: 16759528.9

Publication Number: 3264891

IPC: A01K67/00, A01K67/027, C12N15/00, C12N15/09, C07K14/47

Language of the proceedings: EN

Title of invention:
ETV2 and uses thereof

Applicant:
REGENTS OF THE UNIVERSITY OF MINNESOTA

Headword:
Human-pig chimeras/UNIVERSITY OF MINNESOTA

Relevant legal provisions:
EPC Art. 53(a)
EPC R. 26(1), 28(1)
Vienna Convention on the Law of the Treaties
Directive 98/44/EC of 6 July 1998

Keyword:
Exceptions to patentability - invention contrary to morality (yes)
The Vienna Convention - principle of narrow interpretation of exclusions - no
Category of non-patentable inventions
Human-animal chimeras

Decisions cited:
G 0001/04, G 0002/06, G 0001/07, G 0002/12, G 0001/18, T 0315/03, T 1213/05

Catchword:

Human-animal chimeras and processes to produce them are excluded from patentability in accordance with Article 53(a) EPC if the invention offends against human dignity.
This is the case for instance if it is not excluded that the human cells involved in the chimera integrate into the brain and/or develop into germ cells of the chimera, and result in a chimera with human or human-like capabilities (see point 22 of the Reasons).

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Case Number: T 1553/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 4 September 2024

Appellant: (Applicant)	REGENTS OF THE UNIVERSITY OF MINNESOTA Suite 600, McNamara Alumni Center, 200 Oak Street SE Minneapolis, MN 55455 (US)
Representative:	Lucas, Brian Ronald Lucas & Co. 135 Westhall Road Warlingham, Surrey CR6 9HJ (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 11 February 2022 refusing European patent application No. 16759528.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	D. Luis Alves
	A. Bacchin
	A. Chakravarty
	R. Romandini

Summary of Facts and Submissions

I. The appeal by the applicant (appellant) concerns the decision of the examining division to refuse the European patent application No. 16 759 528.9, entitled "*ETV2 and uses thereof*".

II. The decision under appeal dealt with a main request and auxiliary requests 1 and 2. As regards auxiliary request 2, the examining division held that the claims related to an invention, the commercial exploitation of which was contrary to "ordre public" or morality (Article 53(a) EPC).

III. With the statement of grounds of appeal, the appellant maintained the claim requests on the basis of which the decision under appeal was taken.

IV. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion on the appeal case. The board indicated, *inter alia*, that the claims of auxiliary request 2 encompassed ways of implementing the invention which were regarded as offensive to human dignity, contrary to the requirements of Article 53(a) EPC and that the sole purpose of the oral proceedings would be to hear the appellant on this objection.

Furthermore, the board referred to Kobayashi *et al*, Stem Cell Dev. 24(2), 2015, 182-189, published September 2014 and supplied a copy to the appellant.

V. With the letter dated 12 August 2024, the appellant requested the examination to be based on auxiliary request 2 considered in the decision under appeal, submitted further arguments and a declaration (D16) accompanied by fourteen documents (R1 to R14).

Claims 3 to 5 of auxiliary request 2 read as follows:

"3. A chimeric non-human blastocyst expressing human ETV2 and lacking expression of said non-human animal ETV2, wherein the blastocyst is porcine.

4. A chimeric non-human animal expressing human ETV2 and lacking expression of said non-human animal ETV2 wherein the non-human animal expresses human blood cells selected from the group consisting of white blood cells, red blood cells, platelets or a combination thereof and wherein the chimeric non-human animal is porcine.

5. A method for producing a chimeric non-human animal expressing humanized vasculture [sic] and humanized blood, comprising:
(a) generating an ETV2 null non-human animal cell, wherein both copies of the non-human ETV2 gene carry a mutation that prevents production of functional ETV2 protein in said non-human animal;
(b) creating an ETV2 null non-human blastocyst by somatic cell nuclear transfer comprising fusing a nucleus from said ETV2 null non-human animal cell of (a) into an enucleated non-human oocyte and activating said oocyte to divide so as to form an ETV2 null non-human blastocyst completely lacking the endothelial and hematopoietic lineages and providing a niche for human stem cells to populate;

(c) introducing human stem cells into the ETV2 null non-human blastocyst of (b); and
(d) implanting said blastocyst from (c) into a pseudopregnant surrogate non-human animal to generate a chimeric non-human animal with ETV2 induced humanized vasculture and humanized blood;
wherein said non-human is porcine and the human donor stem cells are pluripotent stem cells, induced pluripotent stem cells or umbilical cord blood stem cells (UCBSC)."

VI. Oral proceedings were held as scheduled in the presence of the appellant. At the end of the oral proceedings, the Chair announced the board's decision.

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

D1: Rashid, T., Cell Stem Cell 15, 2014, pages 406-409
D7: Cyranoski, D., Nature, 26 July 2019
D9: Hashimoto, H. *et al*, Experimental Animals 68(3), 2019, pages 361-370
D10: Garry D.J. and Garry, M.G., Experimental Biology and Medicine 246, 2021, pages 1838-1844
D11: Maeng, G. *et al*, Nature Biomedical Engineering 5, 2021, 7 pages
D11a: Supplementary information to D11, pages 1-21
D15: Kobayashi *et al,* Stem Cells and Development 24(2), 2015, 182-189, published online September 2014
D16: Declaration by Dr Wolf dated 8 December 2024
R1: Wu, J. *et al*, Cell 168, 2017, pages 473-486
R2: Chen, J. *et al*, Proceedings of the National Academy of Sciences of the United States of America 90(10), 1993, pages 4528-32
R3: Identical to D9 above

R4: Identical to D11 above, with pages numbered 805-814
R4a: identical to D11a above
R5: Bender, M. *et al*, Biomedicines 12(6), 2024, 1336 (15 pages)
R6: Reichart, B. *et al*, Cardiovascular Research, 118(18), 2022, 3499-3516
R7: Konstantinov, I.E. *et al*, The Journal of Thoracic and Cardiovascular Surgery 166(3), 2023, 960-967
R8: Längin, M. *et al*, Nature 564, pages 430-433 and annex (13 pages)
R9: Wolf, E. *et al*, Disease Models and Mechanisms, 16(5), 2023, pages 1-7
R10: Reichart, B. *et al*, Transplantation 105(9), 2021, pages 1930-1943
R11: Reichart B *et al*, The Journal of Heart and Lung Transplantation 39(8), 2020, pages 751-757
R12:"Immune Responses to Biosurfaces - Advances in ExperimentalMedicine and Biology 865, editors Lambris *et al*, Springer, 2015, pages 143-155
R13: Bouquet, L. *et al*, Gene Therapy 30(9), 2023, pages 706-713
R14: Ercilla-Rodríguez, P. *et al*, Frontiers in Immunology 15, 2024, pages 1-22

VIII. The appellant's arguments may be summarised as follows:

Main request (auxiliary request 2 considered in the decision under appeal) - Article 53(a) EPC

The examining division's approach to chimeras was unduly restrictive and was not in line with the requirements of Article 53(a) EPC or Rule 26(1) EPC, which provided that Directive 98/44/EC be used as supplementary means of interpretation for patent applications concerning biotechnological inventions.

While Recital 38 of the Directive 98/44/EC referred to the exclusion of chimeras involving human totipotent cells or germ cells from patentability, the claims in suit were directed to blastocysts and methods which involved pluripotent cells.

Moreover, the purpose of the invention was to provide humanised vasculature in swine, suitable for transplantation, rather than providing chimeric animals in which human cells would be found in multiple organs. Article 53(a) EPC was to be construed narrowly. It was the intended exploitation of the invention that was to be taken into account when analysing compliance with the requirements of Article 53(a) EPC (see T 356/93, T 866/01 and T 315/03).

It was the examining division's duty to substantiate an objection under Article 53(a) EPC (see decision T 356/93, reasons 18 to 18.6). Such a substantiation required conclusive evidence, as opposed to hypothetical scenarios.

However, the examining division did not provide evidence that human cells could be found in the claimed chimera other than in the niche corresponding to the deleted porcine gene.

Documents D1, D7, and D9 did not provide conclusive evidence of human cells outside the niche and even indicated that human cells did not participate in the chimera's brain or germ cells (see documents D1, page 408, right-hand column, third paragraph, first and last sentences, D7, page 2, seventh and eight paragraphs and D9, title and discussion at page 369).

The ethical concerns raised in the cited documents were not part of the conclusions drawn from the work reported. Far more they amounted to additional thoughts and were mere speculation.

Only established facts were relevant to the decision to be taken under Article 53(a) EPC. These facts included documents D9 to D11 which provided examples of chimeras in which the cells of the donor species were not found in brain or germ cells (see documents D9, page 369, D10, page 1842 and D11, page 7). Moreover, document R1 demonstrated that human cells did not contribute to a cell lineage outside the niche.

Human cells were either not present outside of the niche or if present would be in insufficient numbers to give rise to offensive characteristics in the chimera. Human cells were at distinct disadvantage in a pig embryo and would not survive (see declaration D16, point 4 and documents R1 to R4), inter alia because of the pig's immune system .

Document R1 did not show that the chimeric embryo would have human characteristics because in fact it did not contain much information on human cells. From Figure 4 it was not possible to conclude whether the human cells would survive in the embryo, because it merely showed the results at 2 days after injection of the human cells into the blastocyst.

Documents R5 to R12 disclosed the usefulness of the invention.

Any concern that human cells would contribute to an organ where they were not desired could be mitigated by further modifying the human cells before introduction

into the pig blastocyst (see declaration D16 and documents R13, R14 and D15).

The board could exercise discretion towards the patent applicant in view of the usefulness of the invention to provide humanised vasculature for transplantation.

Requests

IX. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the sets of claims of auxiliary request 2 considered in the decision under appeal.

Reasons for the Decision

Main request (auxiliary request 2 considered in the decision under appeal)

Background to the invention

1. The application concerns the generation of pig-human chimeric animals with the aim of using them as a source of human vasculature and blood. The chimeric pigs are obtained by methods involving "blastocyst complementation". This involves creating a non-human (host) blastocyst lacking one or more genes involved in the development of the cells of interest. This creates a so-called "niche" which is complemented by introducing into the blastocyst human pluripotent (donor) cells having those lacking genes. Specifically, in the application, the host blastocyst lacks the Etv2 gene, whose function is to promote hematoendothelial development (see application page 1, lines 28 to 30).

2. A blastocyst consists of an outer layer of cells delimiting an inner space which contains the remainder of the cells, designated inner cell mass. The outer cell layer will develop into the placenta while the inner cell mass will develop into all the tissues that form the embryo. The blastocyst is conventionally considered to be a stage of development in which all the cells that make up the inner cell mass do not show any discernable differences and have the potential to develop into every tissue of the embryo. It is only at a subsequent stage of development that the inner cell mass presents a differentiation into three germ layers: endoderm, mesoderm and ectoderm. The cells in these layers no longer have the potential to develop into every tissue of the embryo, as is the case at the blastocyst stage. Neural cells are considered to develop from cells in the ectoderm whereas blood cells, as well as germ cells, will develop from the mesoderm.

The claimed subject-matter

3. Claim 5 is directed to a method of producing a porcine-human chimeric animal expressing humanised vasculature and humanised blood. The method involves complementation of a porcine (host) blastocyst with human (donor) cells. The only feature defining the blastocyst complementation is the limitation of the human donor cells to pluripotent stem cells, induced pluripotent stem cells and umbilical cord blood stem cells. The claim does not define the number of human cells to be introduced into the blastocyst in method step (c) (see Section V. above), nor does it include further characteristics of the human cells.

Claims 3 and 4 are directed to a porcine-human chimeric blastocyst and chimeric animal, respectively, defined

by their expression of human ETV2 and lack of expression of porcine ETV2, and additionally in claim 4 further defined by the expression of human blood cells selected from the list set out in the claim.

Hence, claims 3 and 4 do not include language that would exclude chimeras having human cell participation in the brain or germ cells.

Exceptions to patentability - Article 53(a) EPC

4. The appellant essentially contended that there is no legal basis for the "unduly restrictive approach to chimerism" adopted by the examining division.

5. In the appealed decision, the examining division refused the application for ethical reasons pursuant to Article 53(a) in conjunction with Rule 26(1) EPC and Recital 38 of the Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions (point 4.16 of the Reasons). It also concluded that, although the invention was directed to the genetic modification of animals, the exclusion under Rule 28(1)(d) EPC was not applicable because the outcome of the so-called "balancing test" developed in the jurisprudence for an objection under this provision was in favour of the invention (point 4.18 of the Reasons).

6. A review of the correctness of the examining division's decision in view of the appellant's arguments and newly filed evidence in appeal requires the identification of the applicable legal framework.

Legal framework

7. The ethical dimension of patent law has found its expression in Article 53(a) EPC, together with the implementing regulations in Rules 26 to 29 EPC. These Rules were introduced in the EPC to align the EPC with the Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions (the "EU Biotech Directive"). In order to achieve harmonised protection in the field of biotechnological inventions in Europe, the EU Biotech Directive provides a supplementary means of interpretation for the EPC (Rule 26(1) EPC). Thus, when the compliance of a biotechnological invention with ethical principles has to be assessed, the legal framework is a composite one, in the sense that the EPC provisions should be understood in the light of the EU Biotech Directive, also including considerations which are outside the strict patentability requirements.

8. Article 53(a) EPC expressly addresses exceptions to patentability for reasons of *ordre public* or morality and excludes "*Inventions the commercial exploitation of which would be contrary to "ordre public" or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States*". In the jurisprudence of the Enlarged Board of Appeal and of the Boards of Appeal it was stated that this Article, due to its general wording, embodies overriding legal and ethical norms. Accordingly the concepts of *ordre public* and morality have been identified for instance by reference to constitutional principles, to the European Convention on Human Rights (explicitly mentioned also in Recital 43 of the EU Biotech

Directive), and to the Charter of Fundamental Rights of the European Union.

9. This legal framework, including the EU Biotech Directive (see points 7. and 8. above), requires that patent law is applied so as to safeguard human dignity, as well as further values such as public safety, the integrity of individuals and the protection of the environment.

10. The legislator has further introduced an illustrative list of inventions excluded from patentability in Rule 28(1) EPC which, *in particular*, concerns the following:

(a) processes for cloning human beings;

(b) processes for modifying the germ line genetic identity of human beings;

(c) uses of human embryos for industrial or commercial purposes;

(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

11. This list is non-exhaustive as confirmed both by its wording ("*in particular*") and its scope which, as indicated in the Recital 38 of the EU Biotech Directive (the "Recital 38"), was to "... *also include an illustrative list of inventions excluded from patentability so as to provide national courts and patent offices with a general guide to interpreting the*

reference to ordre public *and morality; whereas this list obviously cannot presume to be exhaustive; ...*".

12. In the jurisprudence of the Boards of Appeal it has also been clarified that an invention falling within one of the categories listed in Rule 28(1) EPC must *ipso facto* be denied a patent under Article 53(a) EPC and there is no need to consider that Article further (see T 315/03, Section 6).

13. Thus as clarified in T 315/03 (Headnotes 2.1, 2.2, Section 6 and 10.1), if an invention corresponds to one of the examples set out in the illustrative list of Rule 28(1) EPC, there is no room for tests aimed at balancing possible risks associated with the implementation of the invention and its benefit for the mankind, as developed by the jurisprudence of the Boards of Appeal for the assessment of an objection under Article 53(a) EPC (so-called "real" Article 53 EPC objection). As an exception, inventions related to the genetic modification of animals under Rule 28(1)(d) EPC, expressly require a particular balancing test between the likelihood of animal suffering and the presence of any substantial medical benefit to man or animal, either in addition or in alternative to the "real" Article 53(a) EPC test (so-called Rule 28(1)(d) type Article 53(a) EPC objection). An example of application of these two tests is given in the preliminary opinion issued by the Board 3.3.08 in case T 682/16.

14. The assessment of objections under Article 53(a) EPC, as well as under Rule 28(1) EPC, should be based on the understanding in the technical field at the relevant date of the patent application, although evidence arising after that date may be taken into account,

provided it reflects the state of the art at the effective date (see decision T 315/03, Reasons 8.2, 9.5, 9.7 and 10.9). The evidence must be conclusive in the sense that it is suitable to show on the overall balance of probabilities, that one set of facts is more likely to be true than the other (see also Case Law of the Boards of Appeal, 10th edition, 2022, III.G.4.3).

15. It is therefore necessary to establish whether the present invention must *ipso facto* be denied a patent, for the same reasons as the categories of inventions illustrated in Rule 28(1) EPC, or whether a further assessment under Article 53(a) EPC, is required.

For this assessment the EU Biotech Directive may provide the context for interpretation in line with Rule 26(1) EPC.

16. Human-animal chimeras are not mentioned in Rule 28(1) (a) to (d) EPC, nor in the provision from which this Rule is derived, namely Article 6(2) of the EU Biotech Directive. However, specific forms of human-animal chimeras are mentioned in Recital 38, which relates to the illustrative list of exclusions for reasons of *ordre public* and morality provided in Article 6(2) of the EU Biotech Directive. Recital 38 includes the following wording:

"...*whereas processes, the use of which offend against human dignity, such as processes to produce chimeras from germ cells or totipotent cells of humans and animals, are obviously also excluded from patentability;*".

17. The appellant argued that the specific prohibition under Recital 38, limited to chimeras from totipotent

cells, would not be sufficient to deny patentability of the present invention, which instead concerns chimeras from pluripotent stem cells and induced pluripotent stem cells (PSC and iPSC). Furthermore, the principle of narrow interpretation of exclusions prevented an extension of the specific form of chimeras beyond the explicit wording of Recital 38.

18. The Board does not agree with this view. As indicated above, the wording of the relevant texts confirm that both Rule 28(1) EPC ("*in particular*") and Recital 38 ("*an illustrative list*", "*cannot presume to be exhaustive*", "*such as processes to produce chimeras from..., are obviously also excluded...*") merely contain a non-exhaustive list of exclusions in order to provide guidance on how to interpret the reference to *ordre public* and morality.

19. Without disregarding the principle of narrow interpretation of exceptions (*singularia non sunt extendenda*), and its particular significance for patent law in order to prevent valuable inventions from being denied patent protection, this board also recognises that in the legal methodology, this principle should be carefully applied (see also Moufang in *Rechtsprechung und Auslegungsmethodik der Großen Beschwerdekammer* des EPA, D.II.5. in Methodenfragen des Patentrechts, publ. von A. Metzger).

The fact that the principle of narrow interpretation cannot generally be applied *a priori* was also acknowledged in more recent decisions of the Enlarged Board of Appeal (see G 2/12, Reasons VI. with reference to G 1/04, Reasons 6: "*..the 'frequently cited principle', according to which exclusion clauses from patentability laid down in the EPC are to be construed*

in a restrictive manner, does not apply without exception"; and to G 1/07, Reasons 3.1: "*Hence, no general principle of narrow interpretation of exclusions from patentability which would be applicable a priori to the interpretation of any such exclusions can be derived from the Vienna Convention. Rather, the general rule in Article 31, point 1 of the Vienna Convention that a treaty shall be interpreted in good faith in accordance with the ordinary meaning to be given to the terms of the treaty in their context and in the light of its object and purpose must apply to the exclusion clauses contained in the EPC in the same manner as to any other provision, the latter including those positively defining the requirements for patentability. If the interpretation of the provision concerned according to these principles of interpretation leads to the result that a narrow interpretation is the right approach then and only then such restrictive meaning is to be given to it.*").

20. In particular, the principle of narrow interpretation of exclusions cannot obviate a necessary analysis of the "object and purpose" of a provision, as also indicated by Article 31 of the Vienna Convention on the Law of the Treaties (Vienna Convention), so that the reasons for the exclusions provided by the legislator cannot simply be disregarded (see G 1/18, Reasons IV.3 and also Moufang in *Münchner Gemeinschaftskommentar*, Art. 53, at point 3).

21. Recital 38 does not exclude chimeras as such, but specifically identifies processes to produce chimeras from germ cells or totipotent cells of humans. Since the present invention involves the use of pluripotent cells, which are distinct from totipotent cells and germ cells, it can be said that Recital 38 does not

apply directly. Nevertheless its underlying rationale can be considered in the application of the general clause of Article 53(a) in conjunction with Rule 28(1) EPC. In this context, the board, far from being tasked with or authorised to arbitrarily define the content of public order and morality, interprets these concepts by reference to pre-existing legal principles and moral norms (as indicated in points 8 and 9 above). Thus, the board relies on the recitals of the EU Biotech Directive, which is a legislative measure adopted by all EU member states and implemented in the EPC contracting states via the EPC. These recitals, like Recital 38, are evidence that a specific ethical value is generally accepted and provide guidance for assessing whether an invention complies with public order and morality.

22. The board takes the view that the exclusion of Article 53(a) in conjunction with Rule 28(1) EPC may extend to other chimeras, where the rationale underlying the examples identified in Recital 38 is also applicable to the chimeras concerned. Thus, by means of Rule 26(1) EPC a further special case is added to the non-exhaustive list of Rule 28(1) EPC.

When considering the possible rationale underlying the specific exclusions of Recital 38, the board finds that the reason why the chimeras identified in Recital 38 are regarded as offensive against human dignity is due to concerns that, in chimeras including human germ cells or totipotent cells, these human cells may integrate into the brain and/or develop into germ cells and result in a chimera with human or human-like capabilities.

This reason is straightforward for chimeras including totipotent cells, which in view of their developmental capability to form an entire organism may form a brain with human-like cognitive abilities or human germ cells. However the same reason applies to pluripotent cells, which despite lacking the ability to differentiate into totipotent cells or cells of the placenta, nevertheless have the ability to differentiate into neural cells or germ cells. Thus, if an invention relates to a situation where human cells might integrate into the chimera's brain, potentially giving the chimera human-like cognitive or behavioural capabilities, or into its germ line, potentially giving it the ability to pass on humanised traits, the board considers that the underlying rationale of Recital 38 of the Directive would be relevant and shall be taken into account in examining compliance with Article 53(a) in conjunction with Rule 28(1) EPC.

23. In view of this conclusion, the board does not consider it necessary to refer to the preparatory work to the EU Biotech Directive. Whereas the recourse to the preparatory work is possible as supplementary means of interpretation under Article 32 Vienna Convention, the board finds that in the present circumstances there is no ambiguous or obscure meaning in the wording of the exclusions in Recital 38 which needs to be clarified, nor does the interpretation on account of its object and purpose lead to a result which is manifestly absurd or unreasonable.

24. With regard to the present case it must therefore be established whether the invention defined in claims 3 to 5 includes embodiments that fall under the scope of Recital 38, thus contravening the requirements of Article 53(a) EPC in conjunction with Rule 28(1) EPC.

Specifically, it must be determined whether the claims define chimeras and methods of producing chimeras including embodiments where human cells participate in the brain or germ cells of the chimera.

25. As set out above (see point 14.), this assessment is to be done on the basis of conclusive evidence, such as scientific publications, rather than on the basis of a hypothetical scenario and such evidence must reflect the state of the art at the effective date. Further, the applicable standard of proof is the balance of probabilities.

The present case

26. As explained below, the board finds that claims 3 to 5, relating to chimeras, are directed to subject-matter which offends against human dignity. This reason alone means that the claimed invention falls under the scope of Recital 38 in contradiction with the requirements of Article 53(a) EPC in conjunction with Rule 28(1) EPC. Even if techniques capable of preventing human cell participation in the brain and/or germ cells of the chimera were available at the effective date, they are not reflected in the technical features of the claims.

27. Document D15 is a scientific article on research into ways of regulating the differentiation of the donor cells into the endodermal organs, in order to address concerns that human cells might be present in the germ line or participate in the brain of chimeras resulting from blastocyst complementation. These ethical concerns are set out prominently in the abstract of the document:

"*Blastocyst complementation, which exploits the capacity of PSCs to participate in forming chimeras, does not, however, exclude contribution of PSCs to the development of tissues — including neural cells or germ cells — other than those targeted ...*".

These concerns are also identified as the motivation for the experiments reported in the document:

"*This fact provokes ethical controversy if human PSCs are to be used. In this study, we demonstrated that forced expression of Mix-like protein 1 ... can be used to guide contribution of mouse embryonic stem cells to endodermal organs after blastocyst injection.*" (see abstract).

In other words, it is stated that without this technique, the cells introduced into the host blastocyst may become part of the germ layers that give rise to the neural cells and germ cells.

28. These ethical concerns are also acknowledged in the patent application in suit, where it is stated : "*It should be noted that parthenogenetic embryos do not survive past 8 weeks, and therefore negates the concern of inadvertently giving birth to undesired human-porcine chimeras.*" (see page 17, lines 22 to 24).

29. Even years after the date of filing of the application, these concerns remained undiminished, as evidenced by documents D9 and D10, which were made available to the public in 2019 and 2021 respectively.

29.1 As can already be seen from the title of document D9, the experiments it reports on address said ethical concerns: "*Development of blastocyst complementation*

technology without contributions to gametes and the brain". These experiments involve blastocyst complementation with mouse embryonic stem cells which have been manipulated to lack expression of *Otx2* and *Prdm14*, considered to be necessary for the formation of the brain and germ cells in mouse, respectively (see abstract and page 369, left-hand column third paragraph to right-hand column, first paragraph). Therefore, this document reports (as does document D15), research into strategies to control the contribution of the donor cells to various tissues in the chimera. It states:

"*... in Japan, it is possible to generate chimeric animals from specified embryos by combining animal blastocysts with human pluripotent stem (PS) cells (animal-human PS chimera). However, the production of animal-human PS chimeras has been restricted because of ethical concerns, such as the development of human-like intelligence and formation of humanized gametes in the animals, owing to the contributions of human PS cells to the brain and reproductive organs. To solve these problems, we established a novel blastocyst complementation technology that does not contribute to the gametes or the brain*" (see abstract).

The ethical concerns are reiterated in the discussion:

"*There is a concern in Japan that blastocyst complementation using human PS cells as donor cells may contribute to the central nervous systems of experimental animals, specifically that the contribution of human stem cells to the brain may lead to the generation of mice with human-like intelligence. Although this may seem unlikely, the possibility cannot be completely ruled out; therefore, it is necessary to address this problem. [...]*

A second concern regarding blastocyst complementation using human stem cells as donor cells is that these cells may contribute to the gametes, leading to the generation of humanized gametes and potentially a new form of life." (see page 369, left-hand column, third and fourth paragraphs).

29.2 According to the appellant, document D9 provides evidence that chimeric blastocyst complementation did not result in participation of human cells in the brain or in the germ line of the chimera. In this context reference was made to the discussion on page 369. A part of the discussion refers to the experimental work reported in Koyabashi *et al*, (see page 369, "Discussion", second sentence, document D15 in the present proceedings)). However, document D15 cannot support the appellant's case for the reasons set out above (see point 27.). As regards the discussion of the experimental work done in document D9, it should be noted that, as is the case for document D15, the work was not done with human donor cells or pig host blastocysts. Notwithstanding this, claims 3 to 5 do not include any features which reflect these approaches to limit donor cell participation in a cell lineage outside the niche. Indeed, while the discussion on page 369 of document D9 concerns the use of donor cells lacking *Pdrm14* and *Otx2* genes in order to address ethical concerns, claims 3 to 5 do not include this limitation. Neither is any such limitation disclosed in the patent application.

29.3 Document D10, which is authored by some of the inventors mentioned in the application in suit, provides an overview on blastocyst complementation techniques and on human-pig chimeras, including chimeras obtained from complementation of pig

blastocysts unable to develop skeleton as well as pig blastocysts unable to develop vasculature and blood cells. It states:

" [...] *for each donor stem cell population used, studies will need to examine their contribution to unintended organs such as the brain or the germ cell lineage. While our recent studies suggested the complete absence of hiPSCs in unintended and nonengineered tissues and organs,[49] these studies will need to be examined for every targeted organ, every host species, and every stem cell population."* (see page 1842, title on left-hand column and text in right-hand column, penultimate sentence).

While the appellant argues that this document provides evidence that human cells were absent from the brain and germ line of the chimera, the board considers the passage as a whole puts the observation of "*complete absence of hiPSCs in unintended and nonengineered tissues and organs*" into perspective when it states that each case must be analysed individually. This in turn makes it clear that the generation of chimeras with hiPSC present in unintended organs was a genuine concern.

30. On the basis of the documents on file and on the balance of probabilities, the board can only conclude that there is no technical reason to dismiss the ethical concerns, raised in the relevant literature, that human cells may be present in the brain or germ cells of a chimera according to the present invention. These concerns are relevant for chimeras resulting from the method defined in claim 5, as well as for the chimeras as defined in claims 3 and 4. This conclusion also takes into account that the method defined in

claim 5 has no limitations as regards either the number of human cells injected in step (c) and that claims 3 and 4 do not include any limitations as to the number of human cells or exclude their presence in the brain or germ line.

31. The appellant argued that the ethical concerns were not driven by science and, where expressed in scientific articles such as D1, D7, D9 and D10, merely followed the established practice of adding afterthoughts to the report of the actual scientific work. These afterthoughts were merely speculative however. Indeed there was no evidence of chimeric embryos or animals with human cells outside of the niche created for the blastocyst complementation. In any case, even if such human cells occurred they would be in small numbers and would have been eliminated by the porcine system, including the immune system.

32. The board does not concur with the appellant that the concerns expressed in scientific articles cited above (see points 27. and 29.) can be dismissed. As set out in point 27. above, document D15 states: "*Blastocyst complementation […] does not, however, exclude contribution of PSCs to the development of tissues — including neural cells or germ cells — other than those targeted* …". This is not expressed as a hypothetical scenario but as a fact.
The board rather sees the research reported in documents D15 and D9 as confirmation that the contribution of human cells to the brain or germ line of the chimera was considered a real possibility. The statement in document D10, that the contribution to unintended organs needs to be examined for each donor stem cell population used, each targeted organ and each host species, despite the observed absence in the

experiments reported, further confirms concerns in the scientific community.

33. The board acknowledges that document D1 while listing ethical concerns associated with chimeras, at the same time dismisses any risks that chimeras with human characteristics would in fact be generated. Nevertheless, weighing all the evidence on file, the board concludes that at the effective date of the patent, the consensus in the art was that generation of such chimeras was a genuine possibility that was not to be dismissed. Such chimeras are not excluded by the terms of the present claims.

33.1 The passage in document D1 cited by the appellant to show that generating a chimera with human characteristics was not perceived as realistic reads as follows (highlights provided by the appellant in grounds of appeal):

"*Though the new approach for generating human organs using livestock animals involves "chimerization" of the blastocyst, we are confident that the above mentioned scenarios would never be realized. From our experimental results [...] Although, as stated above, the reason is not clear [...]Even if we succeed in generating human-mouse chimeras, the contribution of iPSC-derived cells would probably be less than 1% [...] The presence of very small numbers of donor human cells in pig tissue will in our opinion never make a humanized pig unless the relevant organ niche is provided.*" (page 408, right-hand column, last paragraph, underline by the board).

The "scenarios" addressed are generating chimeras with extensive modification of the brain to result in

altered cognitive capacity and behaviours, with human gametes or with human-like appearance (see page 408, right-hand column, second paragraph). The authors dismiss the risk of a pig-human chimera with human characteristics citing their experimental results (second sentence in the cited passage), despite acknowledging that "*the reason is not clear*" (third sentence in said passage), ultimately on the grounds that donor human cells were present in very small numbers in pig tissue.

In the board's view, the third sentence reveals uncertainty about the likelihood of generating a chimera with human characteristics. As can be understood from the last sentence in the cited passage, the authors reached their conclusions due to the presence of only small numbers of donor human cells in the pig tissue. However, the claims before the board are not limited in the number of human cells. Therefore, said last sentence, and the conclusions as a whole in document D1, are not directly applicable to the chimeras and methods as defined in claims 3 to 5.

34. The appellant argued that there was no evidence on file of there ever having been the creation of a chimeric animal having human cells in the brain or germ line. This was because the purpose of the invention was to create chimeric pigs with humanised vasculature suitable for transplantation, rather than provide chimeric animals in which human cells would be found in multiple organs.

However, the relevant legal question is whether or not a porcine-human chimera with human cell participation in the brain or germ cells may result from the blastocyst defined in claim 3, may be included in the

chimeric animals defined in claim 4 or may be generated from the method as defined in claim 5. To answer this question the standard to be applied is the balance of probabilities. As indicated above, neither claims 3 to 5 nor any passage in the description of the present application include any feature directed at limiting donor (human) cell participation in a cell lineage outside the niche. The conclusive evidence before the board in documents D15, D9 and D10 as summarised above leads the board to the conclusion that human cell participation in the brain or germ cells is a realistic possibility, rather than only a hypothetical one (see points 30. and 33.). Accordingly the question is answered in the affirmative.

It thus follows that the examining division was correct to consider that the presently claimed invention falls under the scope of Recital 38. It was therefore the appellant's burden to prove that this was not the case, in particular that the risk of a chimera offensive to human dignity in implementing the invention was avoided.

35. The appellant submitted document R1 to support its argument, also put forward in declaration D16, that human cells do not contribute to a cell lineage outside the niche and that human cells cannot survive in the pig embryo.

35.1 Although no specific passages were referred to, the board understands that the reference is to the abstract, penultimate sentence, which reads: "*We find that naïve hPSCs robustly engraft in both pig and cattle pre-implantation blastocysts but show limited contribution to post-implantation pig embryos*".

35.2 This sentence is however followed by the sentence: "*Instead, an intermediate hPSC type exhibits higher degree of chimerism and is able to generate differentiated progenies in post-implantation pig embryos*".

35.3 Therefore, when read as a whole the abstract discloses that the degree of chimerism depends on the characteristics of the donor human pluripotent stem cells and that in some instances the human cells contribute to multiple lineages in the chimera.

35.4 In addition, this document reveals a large variability in the degree of chimerism even within the same procedure when using the same type of human PSCs. Indeed, the number of human cells in the blastocyst varied from zero to 30, two days after the injection of 10 cells (see figure 4D, right-hand side). This experiment was carried out with porcine blastocysts without a niche, which are considered the most unfavourable conditions for the donor cells to proliferate.

35.5 Therefore, this document does not support the appellant's case, but rather provides evidence of differentiation of the human donor cells into cell lineages outside of the niche. Moreover, it provides evidence of great variability in the proliferation of donor human cells in the pig blastocyst.

35.6 The appellant further referred to document R2 to support the argument that human cells cannot survive in the pig embryo, without however citing a specific passage. The board did not find any passage in this document that supports the argument.

36. The appellant also referred to document D7 to support its argument that human PSCs do not contribute to the brain or germ cells of the chimeric animal. The passages cited report on the complementation technique to generate chimeras with humanised organs of interest. The information content of this document does not go beyond that of document D9 in this context. Thus, for the same reasons as for document D9, it does not provide evidence that chimeric blastocyst complementation does not result in participation of human cells in the brain or in the germ line of the chimera.

37. The appellant's argument that the immune system of the pig would not allow human cells to develop is not pertinent at the development stages in question, i.e. blastocyst stage, where the immune system does not play a role.

38. As further evidence that human donor cells do not contribute to tissues outside the niche, the appellant referred to documents D10 and D11, as disclosing examples of chimeras in which no human cells were detected outside the niche. The contents of document D10 are discussed in point 29.3 above. As argued by the appellant, the cited passage states that hiPSCs did not contribute to the brain or the germ line. Nevertheless, it also makes clear that no conclusions can be drawn for other donor stem cells, targeted organs or other host species. In the board's view, this is directly applicable to the disclosure in document D11, which reports on a chimera with humanised skeletal muscle.

39. In a further line of argument, the appellant pointed to documents R13 and R14 as evidence of approaches to

mitigate any ethical concerns. However, as set out above, these approaches are not reflected in features of the method defined in claim 5 or the chimeras defined in claims 3 and 4. Moreover it was not proven that these approaches, reflected in documents published in 2023 and 2024, were available at the effective date (2016).

40. It is therefore concluded that the appellant has not provided convincing evidence to discard the risks that chimeras with human characteristics would be generated with the present invention.

41. Finally, the appellant stressed also the dramatic importance of the present invention in the field of xenotransplantation, potentially the very first step to repair and replacement technology which was previously regarded as pure science fiction. This fact should be balanced against the unsupported ethical concerns raised by the examining division.

41.1 The board recognises the importance of the present invention. However, for the reasons stated above, balancing tests are irrelevant in the context of the categories of inventions which are excluded from patentability *ipso facto*. Considerations involving balancing the potential benefits of the invention for humanity/the medical benefit against prejudice to human dignity/animal suffering, are limited to the so-called "real" Article 53(a) EPC objections or to inventions related to the genetic modification of animals within the meaning of Rule 28(1)(d) EPC. Instead, where the legislator wanted to exclude inventions offending life and human dignity as such, there can be no room for manoeuvre (see also G 2/06, Reasons 31).

41.2 For the same reason considerations regarding the role of the EPO as patent granting authority, rather than as regulatory authority, cannot be of relevance (see e.g. T 1213/05, Reasons 46 to 57). As the legislator decided to exclude as such certain uses from patentability, national regulatory considerations on research do not play a role.

Conclusion

42. The board finds that the examining division did not adopt an unduly restrictive approach to chimeras. In interpreting Article 53(a) in conjunction with Rule 28(1) EPC, an analysis of the object and purpose of the exclusion according to Recital 38 of the EU Biotech Directive, to be considered under Rule 26(1) EPC, leads to the conclusion that the present invention is excluded from patentability *ipso facto*, for the same reasons as given in Recital 38, because it relates to human-animal chimeras in which human cell participation in the brain or germ cells is a realistic possibility rather than only a hypothetical one.

The claims under examination are not drafted to exclude embodiments in which human cells are present in the brain and/or germ cells of the chimera.

Conclusive evidence based on scientific publications available at or before the priority date shows that the consensus was that creation of chimeras that give rise to ethical concerns were not regarded as merely hypothetical, but were seen as a genuine possibility.

Furthermore, since the claims were not drafted to exclude embodiments where human cells are present in the brain and/or germ cells of the chimera (for instance by the inclusion of features based on technologies capable of preventing the presence of human cells in the brain and/or germ cells of the chimera) the board did not have to decide on the patentability of such subject-matter.

It follows that the claims of auxiliary request 2 do not fulfil the requirements of Article 53(a) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Chavinier M. Pregetter

Decision electronically authenticated