

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BENJAMIN P. CHEN and CHRISTOPHER C. FRASER

Appeal No. 1997-4277
Application No. 08/290,038

ON BRIEF

Before WILLIAM F. SMITH, ROBINSON and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 3-5, 7-9, 11-14 and 16-18, which are all the claims pending in the application.

Claims 1, 5, and 18 are illustrative of the subject matter on appeal and are reproduced below:

1. A mouse host lacking functional syngeneic B-cells and T-cells due to a genetic defect that results in an inability to undergo germline DNA rearrangement at the loci encoding immunoglobulins and T-cell antigen receptors, comprising:
 - a hybrid tissue providing long-term production, for greater than [sic] twenty weeks, of human myeloid cells, B-cells and lymphoid progenitor

cells formed by viable normal human fetal bone fragments and normal human fetal spleen grown in juxtaposition.

5. A method for producing a chimeric mouse capable of long term production, for greater than twenty weeks, of human myeloid cells, B-cells and lymphoid progenitor cells, said method comprising:
 - implanting viable normal human fetal spleen and normal human fetal bone fragments in juxtaposition at a sub-cutaneous site in an immunocompromised mouse host lacking functional syngeneic B- and T-cells due to a genetic defect that results in an inability to undergo germline DNA rearrangement at the loci encoding immunoglobulins and T-cell antigen receptors;
 - whereby said tissue forms a hybrid tissue providing long-term production, for greater than twenty weeks, of human myeloid cells, B-lineage cells and lymphoid progenitor cells.

18. A method for determining the repertoire of lineages that are able to develop from a particular human hematopoietic progenitor cell type, said method comprising:
 - implanting viable normal human fetal spleen, normal human fetal bone fragments and normal human fetal thymus tissue in juxtaposition at a subcutaneous site in an immunocompromised mouse host lacking functional syngeneic B- and T-cells due to a genetic defect that results in an inability to undergo germline DNA rearrangement at the loci encoding immunoglobulins and T-cell antigen receptors;
 - irradiating said hybrid tissue;
 - injected HLA mismatched human hematopoietic progenitor cells into the cavity of said human bone;
 - maintaining said host, whereby said tissue forms a hybrid tissue allowing long-term production, of at least twenty weeks, of human myeloid cells, B-cells and T-cells; and
 - determining the repertoire of lineages of hematopoietic cells that develop having the HLA type of said progenitor cells.¹

¹ We note appellants' Brief contains the following typographical error "determining ... that having" should be "determining ... that develop having." Compare claim 18, Paper No. 7, received January 11, 1996.

Appeal No. 1997-4277
Application No. 08/290,038

The references relied upon by the examiner are:

Namikawa et al. (Namikawa), "Long-term human hematopoiesis in the SCID-hu mouse," J. Exp. Med., Vol. 172, pp. 1055-1063 (1990)

McCune et al. (McCune), "The SCID-hu mouse: a small animal model for HIV infection and pathogenesis," Annu. Rev. Immunol., Vol. 9, pp. 399-429 (1991)

Kyoizumi et al. (Kyoizumi), "Implantation and maintenance of functional human bone marrow in SCID-hu mice," Blood, Vol. 79, No. 7, pp. 1704-1711 (1992)

Mombaerts et al. (Mombaerts), "RAG-1-deficient mice have no mature B and T lymphocytes," Cell, Vol. 68, pp. 869-877 (1992)

GROUND OF REJECTION

Claims 1, 3, 9 and 11 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kyoizumi.

Claims 5, 7, 14 and 16 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kyoizumi in view of McCune and Namikawa.

Claim 13 stands rejected under 35 U.S.C. § 103 as being unpatentable over Kyoizumi in view of McCune.

Claims 4, 8, 12 and 17 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kyoizumi in view of McCune and Namikawa in view of Mombaerts.

Claim 18 stands rejected under 35 U.S.C. § 103 as being unpatentable over McCune in view of Namikawa.

We reverse.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer² for the examiner's reasoning in support of the rejection. We further reference appellants' Brief³ for the appellants' arguments in favor of patentability.

THE REJECTIONS UNDER 35 U.S.C. § 103:

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Claims 1, 3, 9 and 11:

The examiner argues (Answer, page 2) that "Kyoizumi discloses a scid/scid mouse having human fetal bone, human fetal liver and human fetal thymus transplanted and grown in juxtaposition." The examiner recognizes (Answer, page 3) that "Kyoizumi differs from the claims in that the reference fails to disclose the transplantation of fetal spleen." However, the examiner argues [t]he human hematolymphoid organs were known in the art to be spleen, bone, thymus, liver, lymphnodes [sic], skin and omentum." Therefore, the examiner

² Paper No. 16, mailed June 24, 1997.

³ Paper No. 15, received March 19, 1997.

finds (Answer, bridging paragraph, pages 3-4) that “the modification of the mouse of Kyoizumi by also transplanting fetal spleen was within the ordinary skill in the art at the time the claimed invention was made.”

Appellants argue (Brief, page 6) that in contrast to the position taken by the examiner “Kyoizumi *et al.* discloses the results of experiments wherein an immunocompromised *scid/scid* mouse was implanted with a fragment of human fetal bone ... [t]he bone fragments are not implanted in juxtaposition with other tissues, nor is the formation of a hybrid organ structure comprising bone taught or suggested.”

As set forth in Ecolchem Inc. v. Southern California Edison, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fir. Cir. 2000) the:

“[S]uggestion to combine may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved.” ... However, there still must be evidence that “a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.” “[A] rejection cannot be predicated on the mere identification ... of individual components of claimed limitations. Rather particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. [Citations omitted].

Here, the examiner argues (Answer, pages 3-4) that since “[t]he human hematolymphoid organs were know in the art to be spleen, bone, thymus, liver lymphnodes [sic], skin and omentum ... the modification of the mouse of Kyoizumi

by also transplanting fetal spleen was within the ordinary skill in the art at the time the claimed invention was made.” We do not find the evidence and reasoning presented by the examiner sufficient to support a prima facie case of obviousness under 35 U.S.C. § 103.

The examiner relies on Kyoizumi’s concluding remark to provide the necessary suggestion to modify Kyoizumi in a manner to arrive at the claimed invention. However, we do not find Kyoizumi’s speculation (page 1711, first column) that “full reconstitution ... in SCID-hu mice might be achieved by coimplantation ... with other human hematolymphoid organs” [emphasis added] sufficient to provide the requisite suggestion to produce a mouse host as claimed comprising a hybrid tissue formed by bone fragments and spleen grown in juxtaposition. Instead, Kyoizumi’s concluding statement is more a suggestion that one try to obtain full reconstitution of human hematopoietic and immune systems by coimplantation of human BM with other human hematolymphoid organs. “Obvious to try,” however, is not the standard of obviousness under 35 U.S.C. § 103. See In re O’Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

In addition, as appellants explain (Brief, page 9) “[t]he standard for obviousness is ‘whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success’, In re Vaeck, [947 F.2d 488, 493,] 20 USPQ2d 1438[, 1442 (Fed. Cir. 1991)].” We note that claim 1 requires “a hybrid tissue providing long-term production, for greater then [sic] twenty weeks, of human myeloid cells, B-cells and

lymphoid progenitor cells.” As explained by the examiner (Answer page 3), Kyoizumi teaches the transfer of “fetal tissues such as thymus, liver and bone fragments into murine recipients.” However, we find no suggestion, or teaching in Kyoizumi that would provide a reasonable expectation of success that when a mouse comprising “normal human fetal bone fragments and normal human fetal spleen grown in juxtaposition,” “a hybrid tissue providing long-term production, for greater than [sic] twenty weeks, of human myeloid cells, B-cells and lymphoid progenitor cells,” will be obtained as required by claim 1.

Appellants’ specification (page 4) discloses “[t]he spleen tissue appears to amplify to partially or wholly surround the growing human fetal bone and thymus to form a hybrid tissue.” The examiner argues (Answer, page 8) that “[t]his growth of spleen tissue to partially or wholly surround the bone and thymus is not recognized by the specification as being unexpected or novel.” However, the examiner provides no evidence that the prior art would have expected such a hybrid tissue to form. We remind the examiner that “[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.” W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

On this record, the examiner failed to provide the evidence necessary to support a prima facie case of obviousness within the meaning of 35 U.S.C. §103.

Accordingly, we reverse the rejection of claims 1, 3, 9 and 11 under 35 U.S.C. § 103 as being unpatentable over Kyoizumi.

Claims 5, 7, 14 and 16:

The examiner incorporates her previous discussion of Kyoizumi by reference (Answer, page 4) arguing that “Kyoizumi discloses a scid/scid mouse having human fetal bone, human fetal liver and human fetal thymus transplanted and grown in juxtaposition.” The examiner states (Answer, page 4) that “Kyoizumi fails to disclose implantation into a site sub-cutaneously. However ... Namikawa ... and McCune ... cure the deficiency.” The examiner explains (Answer, page 4) that “Namikawa discloses implantation of the fetal thymus and liver under the kidney capsule, which is sub-cutaneously ... [and] McCune discloses that SCID-hu mice are engrafted with component organs of the human hematopoietic system including fetal liver, bone marrow, thymus, lymphnode [sic], spleen, skin and gut.” The examiner finds (Answer, page 4) that “the implantation of multiple components, i.e., fetal liver, spleen, thymus and bone fragments, in juxtaposition is obvious over the transplantation of only several components. [sic] i.e, [sic] thymus and liver as taught by Kyoizumi, and further in view of the suggestion by Kyoizumi to coimplant multiple hematolymphoid components.”

As discussed supra, in our opinion, Kyoizumi fails to provide the requisite suggestion, or expectation of success, to grow normal human fetal bone fragments and normal human fetal spleen in juxtaposition to obtain a hybrid tissue, as required by the claimed invention. Similarly, we find no such suggestion or expectation of

success of obtaining such a hybrid bone/spleen tissue in Namikawa who teach the formation of a unique Thy/Liv structure upon coimplantation of small fragments of human fetal thymus and fetal liver into immunodeficient SCID mice. Furthermore, while as the examiner notes (Answer, page 8) “McCune (page 403, paragraph 3), ... taught that immunodeficient mice can be engrafted with component organs of the human hematopoietic system including human fetal liver, bone marrow, thymus, lymphnode [sic], spleen [sic] skin and/or gut” we find no suggestion, or expectation of success in obtaining a hybrid bone/spleen (claim 5), or bone/spleen/thymus (claim 14), tissue that is capable of long term production of specific human cells as required by the claimed invention. We find no evidence to suggest that a hybrid tissue will form from any tissues other than those of the liver and thymus. We also find no evidence to suggest that even if such a hybrid tissue would form that this new tissue would be capable of “long term production, for greater than twenty weeks,” of human myeloid cells, B-cells and lymphoid progenitor cells (claim 5), or of human myeloid cells, B-cells and T-cells (claim 14).

The examiner is reminded that “[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.” In re Dow Chemical Co. 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In our opinion, on this record, a person of ordinary skill in the art would not have a reasonable expectation of success in obtaining the claimed methods.

Therefore, the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness within the meaning of 35 U.S.C. § 103. Accordingly, we reverse the rejection of claims 5, 7, 14 and 16 under 35 U.S.C. § 103 as being unpatentable over Kyoizumi in view of McCune and Namikawa.

Claim 13:

The examiner argues (Answer, page 5) that:

It would have been obvious to one of skill to modify the host mouse of Kyoizumi by infecting it with HIV-1 in view of the teachings of McCune that a SCID-hu mouse having transplanted human tissues is a useful animal model of human HIV-1 disease and that further work with the animal model may provide additional and novel routes for the analysis of human disease states and their treatment. ... Accordingly, the modification of the mouse of Kyoizumi by infecting the mouse with HIV-1 as suggested by McCune was within the ordinary skill in the art at the time the claimed invention was made.

We remind the examiner that every limitation positively recited in a claim must be given effect in order to determine what subject matter that claim defines. In re Wilder, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970). Here, claim 13 adds the limitation to claim 9, wherein said hybrid tissue is infected with a human tropic virus. While the examiner focused on the “human tropic virus” limitation, the examiner failed to explain how the references relied upon teach or suggest a mouse comprising a hybrid tissue “formed by viable normal human fetal bone fragments, normal human fetal spleen tissue and normal human fetal thymus tissue grown in juxtaposition,” as is required by claim 9.

To the extent that the examiner intends to rely on Kyoizumi for this teaching by stating (Answer, page 5) that claim 13 is “unpatentable over Kyoizumi as applied

to claims 1, 3, 9 and 11 above, and further in view of McCune,” we have discussed the deficiency of Kyoizumi, supra. While not expressly stated, to the extent that the examiner intends that the claimed hybrid tissue would be obvious in view of the combination of Kyoizumi in view of McCune, we find no evidence to suggest that a hybrid tissue would have formed from any tissues other than those of the liver and thymus, when inserted into a mouse. In addition, we find no evidence to suggest that even if a hybrid tissue were to form from bone, spleen and thymus that this new tissue would be capable of “providing long-term production, for at least twenty weeks, of human myeloid cells, B-cells and T-cells.

On this record, we are constrained to reach the conclusion that the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness. Accordingly, we reverse the rejection of claim 13 under 35 U.S.C. § 103 as being unpatentable over Kyoizumi in view of McCune.

Claims 4, 8, 12 and 17:

Claims 4, 8, 12 and 17 depend from claims 1, 5, 9, and 14 respectively and add the limitation “wherein said mouse lacks expression of at least one of functional RAG-1 or RAG-2.” The examiner states (Answer, bridging paragraph, pages 5-6) that:

Claims 1, 3, 5, 7, 9, 11, 14 and 16 were rejected for reasons as stated above. Mombaerts discloses RAG-1 deficient mice and that RAG-1 deficient mice do not have any mature T and B cells. It would have been obvious to one of ordinary skill to modify the method or animal of Kyoizumi by using the RAG-1 deficient mouse of Mombaerts.

As we have stated, supra, Kyoizumi alone or in combination with McCune and Namikawa fail to teach the claimed mouse host, or claimed method of producing a chimeric mouse, comprising a hybrid tissue as claimed. Mombaerts teaching of RAG-1 deficient mice fails to make up for the deficiencies of Kyoizumi or Kyoizumi in view of McCune and Namikawa.

On these facts, the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness within the meaning of 35 U.S.C. § 103. Accordingly, we reverse the rejection of claims 4, 8, 12 and 17 under 35 U.S.C. § 103 as being unpatentable over Kyoizumi or Kyoizumi in view of McCune and Namikawa in view of Mombaerts.

Claim 18:

The examiner argues (Answer, pages 6-7) that:

McCune discloses that human hematolymphoid organs can be reproducibly engrafted into the scid/scid mouse.... McCune differs from the claims in that the reference fails to disclose determining the repertoire of hematopoietic cells which have the HLA type of the progenitor cells. However, ...Namikawa discloses analysis of the 'repertoire' of hematopoietic cells which have the HLA type of said progenitor cells since Namikawa discloses determination of the type of progenitor using antibodies to HLA class I cell surface determinants. ... Accordingly, the modification of the method of McCune by determining the HLA type of the progenitor cells as suggested by Namikawa in order to obtain a method for determining the repertoire of a human hematopoietic progenitor cell was within the ordinary skill in the art at the time the claimed invention was made.

Again, we remind the examiner that every limitation positively recited in a claim must be given effect in order to determine what subject matter that claim

defines. In re Wilder, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970). In

this case, claim 18 is directed to:

A method ... comprising implanting viable normal human fetal spleen, normal human fetal bone fragments and normal human fetal thymus tissue in juxtaposition ... in an immunocompromised mouse ... irradiating said hybrid tissue⁴, injected⁵ [sic] HLA mismatched human hematopoietic progenitor cells into the cavity of said human bone; ... determining the repertoire of lineages of hematopoietic cells that develop having the HLA type of said progenitor cells.

The examiner's focus is on the first and last step of this method. It is, however, unclear from the references relied upon, and the record before us, where the examiner finds a suggestion to irradiate the tissue after it is implanted, and then inject HLA mismatched progenitor cells into the cavity of the implanted human bone as required by the claim.

We remind the examiner that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). On this record, the examiner failed to address all the limitations of the claimed invention. As a result the examiner failed to identify the requisite teaching necessary to support the modification of the prior art to produce the claimed invention.

⁴ We note that the phrase "said hybrid tissue" lacks antecedent support in this claim.

⁵ It appears that appellants' intend "injecting" instead of "injected."

Appeal No. 1997-4277
Application No. 08/290,038

Therefore, the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness within the meaning of 35 U.S.C. § 103. Accordingly, we reverse the rejection of claim 18 under 35 U.S.C. § 103 as being unpatentable over McCune in view of Namikawa.

Appeal No. 1997-4277
Application No. 08/290,038

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the McCune Declaration executed September 28, 1995, relied on by appellants to rebut any such prima facie case.

REVERSED

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WILLIAM F. SMITH)
Administrative Patent Judge)
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) BOARD OF PATENT
DOUGLAS W. ROBINSON)) APPEALS AND
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) INTERFERENCES
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