

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 23

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte JOHN E. DICK, DOUGLAS E. WILLIAMS and TSVEE LAPIDOT

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Appeal No. 1995-2297  
Application 07/797,493

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ON BRIEF

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Before WINTERS, WILLIAM F. SMITH, ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 2, 4, 6-9 and 11-14, all the claims pending in the application. Claims 4, 9 and 13 are representative of the subject matter on appeal and reads as follows:

1. The chimeric mouse of claim 4, wherein said graft is capable of differentiating into multiple lineages of mature human cells and wherein at least 30 % of the hematopoietic cells in bone marrow are of human origin.

4. A chimeric mouse comprising a stable bone marrow graft human hematopoietic cells, wherein the graft is transplanted by a process comprising:
  - a. sublethally irradiating an immunodeficient mouse, wherein the immunodeficient mouse lacks a population of functional T cells and B cells;
  - b. infusing from about  $10^6$  to about  $10^9$  human hematopoietic cells into the immunodeficient mouse; and
  - c. administering an effective amount of human mast cell growth factor (MGF) and a human granulocyte macrophage colony stimulating factor/interleukin-3 fusion protein (GM-CSF/IL-3 FP) to promote engraftment of the human hematopoietic cells.
  
9. A process for engrafting human hematopoietic cells in an immunodeficient mouse comprising:
  - a. irradiating the immunodeficient mouse with from about 5000 to about 10,000 rads/kg body weight;
  - b. infusing from about  $10^6$  to about  $10^9$  human hematopoietic cells per kg body weight to the immunodeficient mouse; and
  - c. administering an effective amount of MGF and GM-CSF/IL-3FP to the immunodeficient mouse which is effective to promote stable engraftment of human hematopoietic cells.
  
13. A chimeric mouse having a stable bone marrow graft of lineage-specific human hematopoietic cells, wherein the population of lineage-specific human hematopoietic cells is selected from the group consisting of erythroid cells, myeloid cells, lymphoid cells and combination thereof, wherein the specific lineage human hematopoietic cells are obtained by a process comprising:

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- a. sublethally irradiating an immunodeficient mouse, wherein the immunodeficient mouse lacks population of functional T cells and B cells;
- b. infusing from about  $10^6$  to about  $10^9$  human hematopoietic cells into the immunodeficient mouse;
- c. administering an amount of MGF and GM-CSF/IL-3 FP which is effective to promote engraftment of the human hematopoietic cells, and an amount of an additional, lineage-specific human growth factor, selected from the group consisting of erythropoietin (EPO), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interleukins-2, -4, -5, -6, and -7, and combination thereof which is effective to promote differentiation and proliferation of the desired lineages of human hematopoietic cells.

The references relied upon by the examiner are:

European Patent Application  
Reisner

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Jul. 24, 1991

Fohlmeister et al. (Fohlmeister), "The Possibility of Assaying Wistar Rat Bone Marrow CFUs in a Xenogeneic (Rat-to-Mouse) System" 4 Cell Growth Regul. pp 221-28 (1985)

Pollard (Pollard), "Protected Environment and its Utility in Experimental Allogeneic and Xenogeneic Bone Marrow Transplantation" 10 (No. 2,3) Tokai J. Exp. Clin Med., pp. 175-79 (1985)

Wade et al. (Wade), "Characterization of Xenogeneic Mouse-To-Rat Bone Marrow Chimeras" 44 (No. 1) Transplantation pp. 88-92 (1987)

McCune, et al. (McCune), "The SCID-hu Mouse: Murine Model for the Analysis of Human Hematolymphoid Differentiation and Function" 241 Science pp. 1632-39 (1988)

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Kamel-Reid et al. (Kamel), "Engraftment of Immune-Deficient Mice with Human Hematopoietic Stem Cells" 242 Science, pp. 1706-09 (1988)

Lubin et al. (Lubin), "Engraftment and Development of Human T and B Cells in Mice After Bone Marrow Transplantation" 252 Science, pp. 427-31 (1991)

#### GROUND OF REJECTION ON APPEAL

Claims 1, 2, 4, 6-9 and 11-14 are rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies upon any one of Pollard, Wade or Fohlmeister taken with McCune.

Claims 1, 2, 4, 6-9 and 11-14 are rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies upon Reisner, Lubin or Kamel.

We reverse the rejection of claims 1, 2, 4, 6-9 and 11-14 under 35 U.S.C. § 103 over Pollard, Wade or Fohlmeister taken with McCune. For reasons discussed herein, we consider claims 1 and 2 separately from claims 4 and 6-8. We affirm the rejection of claims 4 and 6-8 under 35 U.S.C. § 103 over Reisner, Lubin, or Kamel. We reverse the rejection of claims 1, 2, 9, 11 and 12 under 35 U.S.C. § 103 over Reisner, Lubin or Kamel. We vacate the rejection of claims 13 and 14 under 35 U.S.C. § 103

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over Reisner, Lubin or Kamel, and remand this application to the examiner for reconsideration of claims 13 and 14, and to take appropriate action.

#### 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 Answer (Paper No. 17, mailed July 18, 1994) for the examiner's reasoning in support of the rejection. We further reference appellants' Brief (Paper No. 16, filed April 21, 1994) for the appellants' arguments in favor of patentability.

- I. The rejection under 35 U.S.C. § 103 over any one of Pollard, Wade or Fohlmeister taken with McCune.**
- A. Claims 9, 11 and 12 and drawn to a process for engrafting human hematopoietic cells in an immunodeficient mouse comprising.**

As appellants point out, each of Pollard, Wade or Fohlmeister teach "interrodentiary transplants." See, Brief, pages 12 and 13. To overcome the deficiencies in each of the primary references the examiner applies McCune. According to the examiner, McCune "demonstrated the engraftment and differentiation of human tissues in an immune-deficient

mouse host.” See, Answer, page 5. However, as appellants point out, in contrast to the claimed invention, McCune does not irradiate his mice. See, Brief, page 13.

A second distinction noted by appellants is that none of Pollard, Wade, Fohlmeister and McCune mentions the use of growth factors. See, Brief, page 14. In contrast, the claimed invention requires the administration of MGF and GM-CSF/IL-3 FP. At page 11 of the Answer, the examiner states “[i]t is maintained that it would have been obvious and well within the skill of the art to select or assay for human growth factors which would be suitable for administration to a chimeric mouse in order to obtain enhanced engraftment and differentiation of human hematopoietic cells.” We disagree.

What is missing from the examiner’s analysis is a reason or suggestion to administer those factors expressly required by the claim. Specifically, MGF and GM-CSF/IL-3 FP. Without some reason or suggestion to administer MGF and GM-CSF/IL-3 FP, we are left with nothing more than a situation where one would have to vary all parameters trying numerous possible choices until possibly arriving at a successful result where the prior art gave no indication of which parameters were critical and no direction as to which of many possible choices is likely to be successful. “Obvious to try” is not the

standard under § 103. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

**B. Claims 1, 2, 4, 6-8, 13 and 14 are drawn to a chimeric mouse.**

As appellants point out, each of Pollard, Wade or Fohlmeister teach “interrodentiary transplants” in to irradiated mice or rats. See, Brief, pages 12 and 13. To overcome the deficiencies in each of the primary references the examiner applies McCune, to demonstrate “the engraftment and differentiation of human tissues in an immune-deficient mouse host.” See, Answer, page 5. However, as appellants point out, in contrast to the claimed invention, McCune does not irradiate his mice. See, Brief, page 13. Appellants point out that McCune states “[t]o our knowledge, no reports have appeared in which human - -> mouse radiation chimeras have been successfully prepared, by any technique.” See, Brief, page 13 (alteration in original). Appellants continue, citing McCune, at page 13 of the Brief, that “McCune et al. used a system that they felt ‘offers several advantages over the radiation chimera . . . and does not require preparative irradiation’” (alteration in original). The examiner responds by stating “contrary to [a]ppellants’ allegation, the successful demonstration of human cell engraftment in mice by McCune [] would have

certainly motivated one of ordinary skill in the art to prepare additional human-mouse chimera using similar or modified procedures.”

In this instance, McCune teach away from its combination with references teaching radiation chimeras. In addition, the examiner fails to provide a reason, suggestion, or motivation as to why one would combine the references, in lieu of the express teaching away, in a manner that would give rise to appellants’ claimed invention. Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Accordingly we reverse the rejection of claims 1, 2, 4, 6-8, 13 and 14.

**II. The rejection of claims 1, 2, 4, 6-9, and 11-14 under 35 U.S.C. § 103 over Reisner, Lubin or Kamel.**

The position taken by the examiner and the issues raised are similar in regard to the application of Reisner, Lubin or Kamel. Therefore, we address them together below.

**A. Claims 9, 11 and 12 drawn to a process for engrafting human hematopoietic cells in an immunodeficient mouse.**

The examiner recognizes the difference between Reisner and Lubin and the claimed invention at page 4 of the Answer, “[e]ach of these teachings differs from the claimed invention in that . . . human growth factors are not administered to the mouse

host.<sup>1</sup> In addition, the examiner notes that Kamel differs from the claimed invention in that the specific growth factors were not infused at the specific concentrations claimed. See, Answer, page 5. While, recognizing these differences, the examiner maintains that it would be obvious to modify the teachings of either Reisner, Lubin or Kamel by administering effective amounts of human growth factors “in order to obtain enhanced engraftment, differentiation and proliferation of the desired lineages of human hematopoietic cells, with a reasonable expectation of success.” See, Answer, pages 4, 5 and 9.

What is missing from the examiner’s analysis is a reason or suggestion to administer those factors expressly required by the claims. Specifically, MGF and GM-CSF/IL-3 FP. The initial burden of establishing reasons for unpatentability rests on the examiner. See In re Oetiker, 977 F.2d. 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). 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

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<sup>1</sup> The section omitted states “T cell depleted bone marrow from SCID mice is additionally grafted into the irradiated mouse host . . . .” Appellants highlight this difference by stating “bone marrow cells from at least two different sources (SCID mice and human BM cells) were added to another strain of mouse.” Brief, page 6. However, the claimed invention uses the transitional phrase “comprising” which allows for the inclusion of additional cells.

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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). Here, the examiner has failed to state how a person having ordinary skill in the art would have found appellants' claimed invention obvious. Furthermore, in resolving questions of obviousness, the decision-maker must consider the claimed subject matter as a whole. 35 U.S.C. § 103. Here, the examiner has not adequately considered every limitation in the claims in reaching her conclusion of obviousness. Accordingly, the examiner has failed to establish a prima facie case of obviousness. Therefore, we reverse the examiner's rejection of claims 9, 11 and 12 over Reisner, Lubin and Kamel.

**B. Claims 1, 2, 4 and 6-8 are drawn to a chimeric mouse comprising a stable bone marrow graft of human hematopoietic cells.**

Reisner, Lubin and Kamel teach a chimeric mouse having a stable bone marrow graft of human hematopoietic cells. Therefore, according to the examiner, Reisner, Lubin and Kamel each teach the chimeric mouse of claim 4. In response, appellants point out that the bone marrow preparations of Reisner and Lubin were predominantly

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of mouse origin, and human cells account for only approximately 0.3 to 3.0% of the bone marrow in Kamel. See, Brief, pages 6 and 10. Appellants contrast the prior art with the bone marrow of their mice in which at least 30% of the cells are of human origin. See, Brief, pages 6 and 10. We affirm the examiner with regards to claims 4 and 6-8, and reverse the examiner's rejection as it applies to claims 1 and 2.<sup>2</sup>

“Where a product-by-process claim is rejected over a prior art product that appears to be identical, although produced by a different process, the burden is upon the applicants to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Best, 562 F.2d [1252,] 1255, 195 USPQ [430,] 433[ (CCPA 1977)].” In re Marosi, 710 F.2d 799, 803, 218 USPQ 289, 292-93 (Fed. Cir. 1983).

Appellants demonstrate that the bone marrow is comprised of at least 30% human origin. However, as the examiner notes, this distinction over the prior art is not

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<sup>2</sup> We recognize appellant's request that claims 1, 2, 4 and 6-8 stand or fall together, however, upon review of this record, we have determined that claims 1 and 2 can be properly distinguished from claims 4 and 6-8. Therefore, we have considered claims 1 and 2 separate from claims 4 and 6-8.

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commensurate in scope with the invention of claims 4 and 6-8.<sup>3</sup> Claim 1 states “[t]he chimeric mouse . . . wherein at least 30% of the hematopoietic cells in bone marrow are of human origin.” As set forth in Comark Communications Inc. v Harris Corp., 156 F.3d 1182, 1187, 48 USPQ2d 1001, 1005 (Fed. Cir. 1998):

. . . While we recognize that the doctrine of claim differentiation is not a hard and fast rule of construction, it does create a presumption that each claim in a patent has a different scope. “There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant.” Tandon Corp. v. United States Int’l Trade Comm’n, 831 F.2d 1017, 1023, 4 USPQ2d 1283, 1288 (Fed. Cir. 1987).

According to the doctrine of claim differentiation, one would presume that the “at least 30%” limitation found in claim 1, means that claims 4 and 6-8 are of a different scope, for example “[a] chimeric mouse comprising a stable bone marrow graft of human hematopoietic cells.” See, claim 4. Reisner, Lubin and Kamel all teach such a mouse.

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<sup>3</sup> We note that original claims 1-3 contain this “at least 30%” limitation. We also note, that appellants point to this limitation (See, Paper No. 10, filed July 6, 1993, page 4) to overcome the examiner’s rejections under 35 U.S.C. § 102 made in the First Office Action (See, Paper No. 7, mailed December 29, 1992, page 4).

Therefore, we affirm the examiner's rejection of claims 4 and 6-8 over Reisner, Lubin or Kamel.

Claims 1 and 2, however, are commensurate in scope to appellant's evidence establishing an unobvious difference between the claimed product and the prior art product. Therefore, we reverse the examiner's rejection of claims 1 and 2 over Reisner, Lubin and Kamel.

**III. The rejection of claims 13 and 14 under 35 U.S.C. § 103 over Reisner, Lubin or Kamel.**

In our view, the examiner erroneously considered the patentability of the subject matter of claims 13 and 14 under 35 U.S.C. § 103 without first determining the full scope of the subject matter claimed.

Generally, before issues related to the patentability of the claimed subject matter can begin to be considered, the examiner must determine what is being claimed.

[T]he claims must be analyzed first in order to determine exactly what subject matter they encompass. . . .

The first inquiry therefore is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. It is here where the definiteness of the language employed must be analyzed – not in a vacuum, but always in light of the teachings of the prior art and of the particular

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application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.

In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

“Before considering the rejections under 35 U.S.C. § 103 . . . we must first decide . . . [what] the claims include within their scope.” In re Geerdes, 491 F.2d 1260, 1262, 180 USPQ 789, 791 (CCPA 1974).

The specification discloses the ability of a chimeric SCID mouse to produce lineage-specific cells in response to administration of engraftment growth factors and a lineage-specific growth factor. The specification states that the data obtained from Example 6 “suggest that administration of a human engraftment growth factor composition, according to the present invention, supports engraftment of human erythroid precursor cells.” According to appellants, this data “suggests that administration of . . . [the] lineage-specific growth factor EPO support differentiation of the engrafted erythroid precursor cells into mature human red blood cells.” See, Specification, page 14, Example 6. At page 13, of the Specification, Example 5 states “that multiple lineages of myeloid, lymphoid and erythroid cells were present in bone marrow of [appellants’] inventive chimeric SCID mice . . . [and that this] data establish . . . engraftment of human

hematopoietic progenitor cells, particularly of the myeloid, lymphoid, and erythroid lineages.”

In view of this disclosure, the scope of appellants’ claims 13 and 14 is unclear. The claims are drawn to “[a] chimeric mouse having a stable bone marrow graft of lineage-specific human hematopoietic cells . . . .” Appellants’ Examples 5 and 6 demonstrate that the bone marrow graft includes “multiple lineages of myeloid, lymphoid and erythroid cells,” and that administration of a lineage specific growth factor supports the differentiation of engrafted precursor cells into mature cells. Nothing in the claim requires the presence of “mature” cells, thus the lineage-specific human hematopoietic cells claimed can include precursor cells. However, it appears that appellants intend the lineage specific cells to be “mature cells”, see, e.g., Brief, page 10, “only macrophage progenitors were found; no mature cells nor any other lineages were found.” In addition, differentiation in response to a particular lineage specific growth factor does not appear to exclude the presence of other lineages from the “multiple lineages of myeloid, lymphoid and erythroid cells” present in appellants’ graft. See, e.g., Specification, page 13, Example 5. If the term “having” is interpreted as open language the presence of other lineages can be included and bone marrow may meet the limitations of the claim. Therefore, the scope of appellants’ claim

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drawn to a “stable bone marrow graft of lineage-specific human hematopoietic cells” is unclear.

The examiner simply states “that it would have been obvious and well within the skill of the art to select or assay for human growth factors which would be suitable for administration to a chimeric mouse in order to obtain enhanced engraftment and differentiation of human hematopoietic cells.” See, e.g., Answer, page 9. The examiner concludes, “not all the claims recite the argued property. Thus, [a]ppellants’ argument is not commensurate with the scope of the claims and is thus not persuasive.” The examiner’s statements are not sufficient.

A rejection under 35 U.S.C. § 103 requires that obviousness be determined based on the claimed subject matter as a whole. Only when the prior art suggests the subject matter of a claim as a whole, and provides an enabling disclosure as to how one would make the claimed invention, can one properly conclude that the subject matter of a claim would have been obvious under 35 U.S.C. § 103.

The examiner erred in considering the patentability of claims 13 and 14 under 35 U.S.C. § 103 without first “having ascertained exactly what subject matter is being claimed.” In re Wilder, 429 F.2d at 447, 450, 166 USPQ 545, 548 (CCPA 1970).

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In addition, it does not appear that the examiner fully considered the teachings of Reisner at page 12, lines 19-27 of a chimeric mammal having long-term stable xenogeneic hematopoietic cells, having human T lymphocytes, human T and B lymphocytes, cells of the human erythroid cell lineage, or cells of the human myeloid lineage. The examiner also does not discuss the teaching is Kamel of macrophage progenitor cell types, or the teaching of human T cells in Lubin. See, Kamel, page 1707, see also, Lubin page 427.

Accordingly, we vacate the examiner's rejection of claims 13 and 14 as obvious over Reisner, Lubin or Kamel, and we remand the application to the examiner to determine in the first instance the scope of the subject matter claimed. After determining the appropriate scope of the claimed invention the examiner should take a step back and reevaluate the rejection under 35 U.S.C. § 103. If the examiner believes that the claims on appeal are unpatentable under this section of the statute, she should issue an appropriate Office Action setting forth the rejection. In so doing, we urge the examiner to use the model set forth in MPEP § 706.02(j). Adherence to this model will of necessity make the examiner examine the claims on appeal on an individual basis, using the correct legal standards.

CONCLUSION

1. We reverse the examiner's rejection of claims 1, 2, 4, 6-9 and 11-14 under 35 U.S.C. § 103 over any one of Pollard, Wade or Fohlmeister taken with McCune.
2. We reverse the examiner's rejection of claims 1, 2, 9, 11 and 12 under 35 U.S.C. § 103 over Reisner, Lubin or Kamel.
3. We affirm the examiner's rejection of claims 4 and 6-8 under 35 U.S.C. § 103 over Reisner, Lubin or Kamel.
4. We vacate and remand the examiner's rejection of claims 13 and 14 under 35 U.S.C. § 103 over Reisner, Lubin or Kamel.

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This application, by virtue of its “special” status, requires an immediate action.  
Manual of Patent Examining Procedure (MPEP) § 708.01(d)(7<sup>th</sup> ed., rev 1, February 2000).

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART and REMANDED

SHERMAN D. WINTERS	)	
Administrative Patent Judge	)	
	)	
	)	
	)	
WILLIAM F. SMITH	)	BOARD OF PATENT
Administrative Patent Judge	)	APPEALS AND
	)	INTERFERENCES
	)	
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