

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte GEORGE NORBERT COX III, CASEY CHRISTOPHER CASE,
STEPHEN P. EISENBERG, ERIC EDWARD JARVIS and
SHARON KAYE SPRATT

Appeal No. 2006-1270
Application No. 10/222,614

ON BRIEF

Before GRIMES, GREEN, and LEBOVITZ, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 114, 116 and 119-124, all of the pending claims. Claims 114 and 120-124 are representative of the claims on appeal, and read as follows:

114. A cell comprising first and second engineered zinc finger proteins, where each of the zinc finger proteins further comprises an endonuclease or functional fragment thereof, and further wherein:
(a) the first protein binds to a first target site; and
(b) the second protein binds to a second target site.

120. The cell of claim 114, wherein the cell is an animal cell.

121. The cell of claim 120, wherein the cell is a mammalian cell.

122. The cell of claim 121, wherein the cell is a human cell.
123. The cell of claim 122, wherein the cell is a stem cell.
124. The cell of claim 123, wherein the cell is a hematopoietic stem cell.

Claims 123 and 124 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In addition, Claims 114, 116 and 119-122 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Brenneman¹ and Chandrasegaran.² After careful review of the record and consideration of the issues before us, we reverse both rejections.

DISCUSSION

Claims 123 and 124 stand rejected under 35 U.S.C. § 112, first paragraph, “as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.” Examiner’s Answer, page 3.

¹ Brenneman et al. (Brenneman), “Stimulation of intrachromosomal homologous recombination in human cells by electroporation with site-specific endonucleases,” PNAS, Vol. 93, pp. 3608-12 (1996).

² Chandrasegaran, U.S. Pat. No. 5,792,640, issued August 11, 1998.

“[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original). “[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.” Id. at 224, 169 USPQ at 370. Here, the examiner has not provided “acceptable evidence or reasoning which is inconsistent” with the specification, and therefore has not met the initial burden of showing nonenablement.

The examiner engages in a Wands analysis, see In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988) (noting that facts that should be considered in determining whether a specification is enabling include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims) to come to the conclusion that it would require

an undue amount of experimentation to make and/or use the claimed cells, wherein the cells are stem cells. See Examiner's Answer, pages 3-6.

The examiner notes that there are no working examples, and that the "specification provides guidance to use zinc finger-endonuclease fusion proteins as gene regulators . . . and as transcription repressors . . . without further elaboration as to how such functions can be achieved." Id. at 4. Those are issues that would seem to apply to the use of any cell type, not just stem cells, and the examiner does not explain how those issues provide more of an impediment to the use of stem cells as opposed to other cell types.

With respect to stem cells, the examiner focuses on the use of the zinc finger-endonuclease constructs in homologous recombination in stem cells. See id. at 4. The examiner cites Hatada³ for the proposition "that hematopoietic stem cells have not been shown to perform homologous recombination." Id. Hanson⁴ is cited for demonstrating that "hematopoietic stem cells are difficult to purify and manipulate." Id. at 4-5. Finally, Zwaka⁵ is cited for the discussion that "human embryonic stem cells are more difficult to manipulate than prior art mouse embryonic stem cells," and that it does not appear that homologous

³ Hatada et al. (Hatada), "Gene correction in hematopoietic progenitor cells by homologous recombination," PNAS, Vol. 97, No. 25, pp. 13807-811 (2000).

⁴ Hanson et al. (Hanson), "Enhanced green fluorescent protein targeted to the Sca-1 (*Ly-6A*) locus in transgenic mice results in efficient marking in hematopoietic stem cells *in vivo*," Experimental Hematology, Vol. 31, pp. 159-67 (2003).

⁵ Zwaka et al. (Zwaka), "Homologous recombination in human embryonic stem cells," Nature Biotechnology, Vol. 21, pp. 319-21 (2003).

recombination was known in any other human stem cell at the time of its publication. Id. at 5.

The examiner also states that

[t]he prior art does not show human stem cells with zinc finger-endonuclease fusion proteins, the prior art therefore does not predict whether such cells could be made or used. Hatada [] shows that stem cells are difficult to isolate, Hanson [] shows that hematopoietic stem cells are difficult to purify and manipulate, and Zwaka [] show[s] that human embryonic stem cells are difficult to manipulate.

Id.

As noted by appellants, see Appeal Brief,⁶ page 5, the Hatada and Zwaka references relate to homologous recombination, and the claims are not limited to cells containing two engineered zinc finger proteins that also comprise an endonuclease, that are required to undergo homologous recombination. Cells comprising a single zinc finger-nuclease fusion protein, appellants assert citing Chandrasegaran, “were known to be useful in mutagenesis, targeted cleavage, gene expression, detection of conformational changes in nucleic acid and targeted recombination.” Reply Brief, page 4. Thus, Hatada and Zwaka, as they relate to the frequency of homologous recombination in human stem cells, are not relevant to the issue of whether claims 123 and 124 are enabled by the specification. Moreover, while Zwaka teaches that electroporation protocols that have been developed for mouse embryonic stem cells do not achieve the same results in human embryonic stem cells, see id., abstract, the reference teaches further that “[f]or human embryonic stem cells, the best chemical reagents yield

stable (drug-selectable) transfectants at rates about 10^{-5} , " id. at page 319, first column, second full paragraph. Thus, Zwaka teaches that human embryonic stem cells may be transfected through the use of chemical reagents.

Moreover, while Hanson teaches that "[e]xperimental manipulation of hematopoietic stem cells is challenging . . . [as] [t]hey are difficult to purify, propagate ex vivo, assay, and transduce," id. at 159, second column, Hanson also teaches that enhanced green fluorescent protein was integrated into the Sca-1 (glycosyl phosphatidyl-anchored protein) locus by homologous recombination in mouse embryonic stem cells, see id., abstract. Thus, Hanson demonstrates while it may be difficult to manipulate hematopoietic stem cells, it is possible to do so. See, e.g., Johns Hopkins University v. CellPro, Inc., 152 F.3d 1342, 136-61, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998) ("The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." (insert in original)).

Finally, the fact that the prior art does not show human stem cells with zinc finger-endonuclease fusion proteins is not the correct standard to measure enablement, for if it were, any novel and/or non-obvious invention would be, by definition, non-enabled.

⁶ All references to the "Appeal Brief" are to the Appeal Brief dated July 11, 2005.

Therefore, as the examiner has failed to set forth a prima facie case of unpatentability under 35 U.S.C. § 112, first paragraph, we are compelled to reverse the rejection.

Claims 114, 116 and 119-122 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Brenneman and Chandrasegaran.

The panel would first like to note that the rejection is premised on an incorrect claim construction.

Claim 114 is drawn to “[a] cell comprising first and second engineered zinc finger proteins, where each of the zinc finger proteins further comprises an endonuclease or functional fragment thereof, and further wherein: (a) the first protein binds to a first target site; and (b) the second protein binds to a second target site.”

According to the examiner, “[t]he phrase ‘A cell comprising first and second engineered zinc finger proteins’ . . . is interpreted to include cells with two identical zinc finger proteins. The phrase ‘(a) the first protein binds to a first target site; and (b) the second protein binds to a second target site’ . . . is interpreted to include two identical zinc finger target sites.” Examiner’s Answer, page 6.

The problem with the examiner’s construction is that it is reading the limitations “first and second engineered zinc finger protein” and “a first target site” and “a second target site” out of the claims. We construe “first and second engineered zinc finger protein” as two distinct and different zinc finger proteins, and construe “a first target site” and “a second target site” as two distinct and

different target sites. Now that the claims have been construed, we now turn our attention to review of the obviousness rejection.

Brenneman is cited for disclosing “that the efficiency of homologous recombination in a human cell can be increased by digestion by an endonuclease at the site of homology.” Examiner’s Answer, pages 6-7. Brenneman specifically teaches that *Xba* I endonuclease, as well as the rare-cutting yeast endonuclease PI-Sce I increased the frequency of recombination, whereas restriction enzymes that cut outside of the repeated regions or between them “produced no change in recombination frequency.” Brenneman, abstract. The examiner notes that “Brenneman [] does not show use of a chimeric nuclease that comprises a zinc finger protein.” Examiner’s Answer, page 7.

Chandrasegaran is cited for disclosing “bacterial cells transformed with a fusion protein of a three-zinc finger DNA binding domain linked to a catalytic nuclease domain of Fok I.” Id. Chandrasegaran is also cited for teaching that each finger of the zinc finger protein binds to three nucleotides of a polynucleotide, and that zinc finger proteins may be designed to bind a series of triplet nucleotides of choice. See id.

The examiner concludes:

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the endonuclease used by Brenneman [] by use of the chimeric zinc finger-Fok I endonuclease of Chandrasegaran because use of the endonuclease of Chandrasegaran allows for cleavage at other repeated sites of choice and would thereby increase the frequency of homologous recombination at the sites of choice. Recombination at repeated sites of choice would further enable generation of desired recombination products and allow for further

study of the process of homologous recombination as exemplified by the experiments of Brenneman. Brenneman [] shows that cleavage at two repeated sites in a target sequence for homologous recombination increases the rate of homologous recombination, and further shows a large repeated sequence as a substrate for homologous recombination. Chandrasegaran shows that a chimeric zinc finger-Fok-I endonuclease may be designed to specifically bind to a sequence of 9 base pairs and that it is possible to design the zinc finger portion to bind to a target sequence of choice. It is further obvious from consideration of the effect of expression of endonucleases on cell viability in both Brenneman [] and Chandrasegaran that the lethality of the endonuclease used by both groups is due to cleavage at multiple sites in the host cell chromosome, especially in view of the observation by Brenneman [] that the rare-cutter PI-Sce I is not lethal to the host cell. Therefore both the cells of Brenneman [] and Chandrasegaran show cells with multiple target sites for endonucleolytic cleavage.

Id. at 8.

Appellants argue that “[n]owhere do the cited references, alone or in combination, teach or suggest the cells including two chimeric zinc fingers as claimed.” Appeal Brief, page 9. Moreover, appellants assert that “the Examiner’s interpretation that the claims ‘include cells with two identical zinc finger proteins’ and ‘two identical zinc finger target sites’ is not correct . . . [as] throughout prosecution, Appellants have repeatedly characterized the claimed subject matter as relating to ‘cells comprising two zinc finger proteins of different sequence.’” Reply Brief, page 8. We agree, and the rejection must be reversed.

As we have stated above, the examiner’s rejection is based on an erroneous claim construction. And as the examiner has not pointed to how the references as combined teach or suggest a cell comprising two different

engineered zinc finger proteins, wherein each protein also comprises an endonuclease, we are compelled to reverse the rejection.

CONCLUSION

Because the examiner has failed to set forth a prima facie case of unpatentability, both rejections of record are reversed.

REVERSED

Eric Grimes)
Administrative Patent Judge)
)
)
)
) BOARD OF PATENT
Lora M. Green)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
)
Richard M. Lebovitz)
Administrative Patent Judge)

Sean Brennan
Sangamo BioSciences, Inc.
501 Canal Blvd.
Suite A100
Richmond CA 94804