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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PHILLIPE DUCHATEAU, CHRISTOPHE PEREZ, SYLVIA BRUNEAU, JEAN-PIERRE CABANOLIS, JULIANNE SMITH, and AGNES GOUBLE

Appeal 2018-007697
Application 15/080,232
Technology Center 1600

Before DEBORAH KATZ, JOHN G. NEW, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 17–39. We have jurisdiction under 35 U.S.C. § 6(b).

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Cellectis S.A. Appeal Br. 1.

We AFFIRM.[2]

STATEMENT OF THE CASE

"The present invention relates to the use of meganucleases for inducing homologous recombination *ex vivo* and *in toto* in vertebrate somatic tissues and to its application for genome engineering and gene therapy." Spec. 1.

Claims 17–39 are on appeal. Claim 17 is representative and reads as follows:

> 17. A method of cleaving a targeted double stranded DNA sequence in a liver cell of a mammal *in toto*, the method comprising steps of:
>
> (a) injecting intravenously into the mammal a vector comprising a nucleic acid sequence encoding a custom-made meganuclease that specifically recognizes and cleaves the targeted double stranded DNA sequence, where the nucleic acid sequence is operably linked to an expression control sequence and the targeted sequence comprises a recognition site which is 12 to 60 bp in length and comprises the cleavage site, and
>
> (b) wherein a double strand break is induced in the targeted double stranded DNA sequence by the custom-made meganuclease in the liver cell.

The claims stand rejected as follows:[3]

[2] We have considered and herein refer to the Specification of Mar. 24, 2016 ("Spec."); Final Office Action of Mar. 6, 2017 ("Final Act."); Appeal Brief of Dec. 5, 2017 ("Br."); Examiner's Answer of June 25, 2018 ("Ans."); and Reply Brief July 19, 2018 ("Reply Br.").

[3] Claims 29 and 33 were rejected under 35 U.S.C. §112, second paragraph as indefinite. Final Act. 3. The Examiner withdrew this rejection. Advisory Act. mailed Nov. 24, 2017.

Claims 17–39 have been rejected under 35 U.S.C. § 112, first paragraph as not enabled.

Claims 17, 19–-22, 24, 26–32, 34–37, and 39 have been rejected under 35 U.S.C §103(a) as unpatentable over Arnould[4] in view of Draper[5] or Norris.[6]

ENABLEMENT

The issue with respect to this rejection is whether the Specification teaches those skilled in the art how to make and use the full scope of the invention.

The Examiner finds that the Specification discloses a method whereby a vector encoding for scI-CreI is injected directly into a liver cell. Final Act. 4–5. The Examiner finds that the claims are directed to the use of meganucleases broadly and injection the vector intravenously. *Id.* at 6.

The Examiner finds that the Specification is not enabling for the route of administration recited in the claims.[7] *Id.* at 11. The Examiner finds that the art teaches that intravenous administration of meganucleases is

[4] Arnould et al., US 2004/0002092 A1, published Jan. 1, 2004 ("Arnould").
[5] Draper et al., US 2004/0054156 A1, published Mar. 18, 2004 ("Draper").
[6] Norris et al., US 2004/0220123 A1, published Nov. 4, 2004 ("Norris").
[7] In the Final Action, the Examiner also based his rejection for lack of enablement on the lack of any teaching as to how to prepare generic meganucleases having the properties recited in the claims. Final Act. 5–11. In the Answer, the Examiner stated that "[t[he main remaining issue is the lack of enablement of administration means of administering nucleic acids intravenously and having them reach their target" in an amount to be effective. Ans. 5. As the Examiner appears to have withdrawn the rejection relating to the creation of the meganucleases, we shall limit our discussion to the issue of intravenous administration of the meganucleases.

unpredictable and that IV administration of the single species described in the Specification would not enable one skilled in the art to use IV administration for all meganucleases falling with the scope of the claims. *Id.* at 12.

The Examiner concludes:

> Given the large size and diversity of meganucleases and the inability to determine which will also have the essential element, it is concluded that the invention must be empirically determined. To that end the breadth of the claims simply embodies too many non-operative embodiments from which undue experimentation would be required to identify those that are functional. In an unpredictable art, the disclosure of no species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/functional characteristics of variants, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Id. at 13.

In response Appellant contends that the Specification is enabling for the full scope of the claims. Appeal Br. 2. In support of this contention, Appellant cites to the Declaration of Dr. Duchateau[8] where he testifies that it based on the teachings in the art and the guidance in the Specification, it would be a matter of routine experimentation to intravenously inject a

[8] Declaration of Dr. Phillipe Duchateau Under 37 C.F.R. § 1.132, filed Nov. 7, 2016 ("Duchateau Decl.").

custom made meganuclease in a mammal such that the meganuclease is expressed in the liver. Duchateau Decl. ¶¶ 11–14.

Appellant contends that the references cited by the Examiner do not teach that IV administration for expression in the liver is uncertain and would require undue experimentation to achieve success. Appeal Br. 5–6. Appellant contends that one of the references, Cox[9], teaches that in vivo editing can be successfully performed in the liver. Appeal Br. 6, citing Cox, 127.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).

We have considered the arguments advanced by the Examiner and Appellant and conclude that the Examiner's rejection is not in error. As the Examiner points out, the claims before us are very broad, in that they cover the intravenous administration of a vector encoding for any custom meganuclease. Ans. 4–5. While the Specification teaches intravenous administration in mice, we find nothing in the record which would lead one skilled in the art to conclude that it would be a routine matter to intravenously administer the same meganuclease containing vector to a larger mammal such as a human. The Examiner points out the specific problems encountered when translating from mice to humans including dose variability and ensuring that the nucleic acids reach their target. Ans. 6–7.

[9] Cox, B. et al. (2015), Therapeutic genome editing: prospects and challenges, *Nature Med. 21*:121–131.

For example, Cox lists some of the problems which may have been countered, including development of an immune response to the large amount of vector required for treatment and controlling the distribution of the meganucleases such that off-target mutations are avoided. Cox, 127. Similarly, Wang teaches that "clinical application of these programmable nuclease complexes are hampered by their inability to reach the intended target tissue, cross the cell membrane, and exert their therapeutic activities *in vivo*." Wang, 1–2.

Although we agree with Appellant that Cox teaches that viral vectors have been used to deliver gene editing therapies to liver tissue, the present claims are not limited to viral vectors but encompass any vector. In addition, while Cox teaches that the editing was accomplished in vivo, Cox does not state whether the vector was administered intravenously or directly into the tissue. *See* Cox, 126–127.

Dr. Duchateau's declaration is not persuasive. The examples discussed in paragraph 11 of the declaration only address intravenous administration to mice. Duchateau Decl. ¶ 11, Spec. 71–79. The Declaration also make it clear that the articles discussed in paragraphs 12 and 13 are limited to mouse models. *See id.* ¶¶ 11 and 12. (Liu reports the delivery of genes to the livers of mice and Zang reports delivery by tail vein injections). Thus, Dr. Duchateau's declaration does not contain any evidence that mouse models are translatable to humans or other mammals.

We conclude that the Examiner's finding with regard to enablement is correct. The Examiner has properly stated reasons which support the conclusion of non-enablement. Appellant has not presented an evidence to show that one skilled in the art would understand that intravenous

administration of any vector containing a meganuclease in a mammal other than a mouse can be done without undue experimentation based solely on data from models based on mice.

OBVIOUSNESS

The issue with respect to this rejection is whether a preponderance of the evidence supports the Examiner's conclusion that the subject matter of the claims would have been obvious over Arnould combined with Norris and Draper.

The Examiner finds that Arnould teaches a method for inducing genetic recombination in the liver of a vertebrate comprising IV administration of a meganuclease coding sequence. Final Act. 17. The Examiner finds that Arnould teaches targeting a vector to delete part or all of a genome and that the meganuclease can be a hybrid. *Id.*

The Examiner finds that while Arnould does not teach that the target cell is the liver, Norris and Draper teach the use of a catalytic nucleic acid to remove hepatitis B virus from the liver. *Id.* The Examiner concludes

> it would have been obvious to one of ordinary skill in the art at the time the invention was made to improve the treatments of Norris and Draper et al by addition of a meganuclease as taught by Arnould et al because Norris and Draper et al teach that it is within the ordinary skill of the art to target virus in the liver and because Arnould et al teach that it is within the ordinary skill of the art to use meganuclease with such methods. One would have been motivated to do so in order to receive the expected benefit of improved recombination. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Id. at 18.

Appellant contends that one of ordinary skill in the art would not have combined the teachings of Arnould with Norris or Draper. Appeal Br. 9. Appellant contends that both Norris and Draper target viral RNA whereas the meganucleases target DNA. *Id.* Appellant argues:

> One of ordinary skill in the art would not have found a suggestion in Draper or Norris to target viral *DNA* in liver cells, since there is no mention of targeting DNA in *any* cells in Draper and Norris, much less in liver cells. Without such a suggestion to target DNA in liver cells, there would be no motivation to choose Arnould for combination with Draper and Norris, since it is well known in the art that meganucleases target DNA, not RNA.

Id.

"Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). "Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.*

We have considered the arguments advanced by Appellant and the Examiner and find that Appellant has the better position.

Arnould teaches the use of meganucleases to cleave or delete a viral genome to treat or prevent a condition or disorder. Arnould ¶¶ 227, 230. Arnould specifically targets viral DNA sequences. *Id.* ¶ 226. Arnould is silent as to treatment of viruses in the liver. Arnould ¶ 227.

Draper and Norris teach the use of ribosomes or phages to disrupt the action of viral RNA. Draper, Abstract; Norris ¶ 23. Draper and Norris teach that the agents are effective against Hepatitis B virus ("HBV"). Draper, Abstract; Norris ¶ 28.

We agree with Appellant that none of the references teach or suggest targeting viral DNA in liver cells. As Appellant points out, Draper and Norris are directed to reducing the expression and spread of HBV by acting on the RNA expressed by the virus but do not affect the HBV DNA. Reply Br. 9–10. Nothing in either reference suggests acting on the viral DNA present in the liver cells. We agree with Appellant that absent such a teaching, one skilled in the art would not have been motivated to use the meganucleases of Arnould to target viral DNA in liver cells as recited in the claims.

The Examiner contends that both Draper and Norris teach the need to cleave HBV in liver cells. Ans. 14. We do not agree. As discussed above, Draper and Norris act on the RNA expressed by HBV in an effort to reduce expression and spread of the virus. The Examiner has not pointed to any specific teaching in either Draper or Norris which calls for acting on the DNA of the HBV so as to cleave or remove the viral DNA from liver calls.

We conclude that a preponderance of the evidence does not support the Examiner's conclusion that the subject matter of the claims would have been obvious over Arnould combined with Draper and Norris.

CONCLUSION

In summary:

Claims Rejected	Basis	Affirmed	Reversed
17–39	35 U.S.C. §112, first paragraph - Enablement	17–39	
17–39	35 U.S.C. §103(a) Arnould combined with Draper and Norris		17–39
Overall Outcome		17–39	

No time for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED