

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 53

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte JAN ZAVADA, SILVIA PASTOREKOVA and
JAROMIR PASTOREK

Appeal No. 2001-1970
Application No. 08/260,190

ON BRIEF

Before WILLIAM F. SMITH, SCHEINER, and GRIMES, Administrative Patent Judges.

GRIMES, 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 30, 32, 35-37, and 39-48, all of the claims remaining.

Claims 30, 32, and 36 are representative and read as follows:

30. A method of treating neoplastic disease and/or pre-neoplastic disease in a vertebrate, wherein said disease is associated with abnormal MN gene expression comprising inhibiting the expression of MN gene by administering a MN antisense oligonucleotide in a physiologically acceptable carrier, wherein said MN antisense oligonucleotide is complementary to SEQ ID NO: 5.

32. A method according to Claim 30 wherein said MN antisense oligonucleotide is complementary to the 5' end of the mRNA that is transcribed from the complement of SEQ ID NO: 5.

36. A method according to Claim 30 wherein said MN antisense oligonucleotide is selected from the group consisting of SEQ ID NOS: 3, 4 and 7.

The examiner relies on the following references:

- Hoke et al. 5,585,479 Dec. 17, 1996
- Wagner, "Gene Inhibition using Antisense Oligodeoxynucleotides," Nature, Vol. 372, pp. 333-335 (1994)
- Rojanasakul, "Antisense Oligonucleotide Therapeutics : Drug Delivery and Targeting," Advanced Drug Delivery Reviews, Vol. 18, pp. 115-131 (1996)
- Gura, "Antisense Has Growing Pains," Science, Vol. 270, pp. 575-577 (1995)
- Reynolds, "First Antisense Drug Trials Planned In Leukemia," Journal of the National Cancer Institute, Vol. 84, pp. 288-289 (1992)
- Stein et al., "Antisense Oligonucleotides as Therapeutic Agents – Is the Bullet Really Magical ?" Science, Vol. 261, pp. 1004-1012 (1993)
- Wu-Pong, "Oligonucleotides: Opportunities for Drug Therapy and Research," Pharmaceutical Technology, Vol. 18, pp. 102-114 (1994)
- Stull et al. (Stull), "Antigene, Ribozyme and Aptamer Nucleic Acid Drugs : Progress and Prospects," Pharmaceutical Research, Vol. 12, pp. 465-483 (1995)
- Milligan et al., "Current Concepts in Antisense Drug Design," Journal of Medicinal Chemistry, Vol. 36, No. 14, pp. 1923-1937 (1993)
- Branch, "A good antisense molecule is hard to find," TIBS, Vol. 23, pp. 45-50 (1998)
- Tseng et al., "Antisense Oligonucleotide Technology in the Development of Cancer Therapeutics," Cancer Gene Therapy, Vol. 1, No. 1, pp. 65-71 (1994)
- Miller et al., " Gene Transfer and Antisense Nucleic Acid Techniques," Parasitology Today, Vol. 10, No. 3, pp. 92-97 (1994)
- James, "Towards Gene-Inhibition Therapy: A Review of Progress and Prospects in the Field of Antiviral Antisense Nucleic Acids and Ribozymes," Antiviral Chemistry & Chemotherapy, Vol. 2, No. 4, pp. 191-214 (1991)

Westermann et al., "Inhibition of expression of SV40 Virus Large T-Antigen by Antisense Oligodeoxyribonucleotides," Biomed. Biochim. Acta, Vol. 48, No. 1, pp. 85-93 (1989)

Orkin et al., "Report and Recommendations of the Panel To Assess the NIH Investment in Research on Gene Therapy," NIH Report on Gene Therapy (1995)

Friedmann, "Overcoming the Obstacles," Scientific American, pp. 96-101 (June 1997)

Mastrangelo et al., "Gene Therapy for Human Cancer: An Essay for Clinicians," Seminars in Oncology, Vol. 23, No. 1, pp. 4-21 (1996)

Weiss, "Upping the Antisense Ante," Science News, Vol. 139, pp. 103-109 (1991)

Claims 30, 32, 35-37, and 39-48 stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled.

We reverse.

Background

The specification discloses that a "quasi-viral agent having rather unusual properties was detected by its capacity to complement mutants of vesicular stomatitis virus. . . . The quasi viral agent was called MaTu." Page 2. "MaTu was found by the inventors to be a two-component system, having an exogenous transmissible component, MX, and an endogenous cellular component, MN." Id. The "MX" component was later identified as lymphocytic choriomeningitis virus (LCMV). See the specification, page 3.

"[T]he MN component was found to be a cellular gene, showing only very little homology with known DNA sequences. The MN gene was found to be present in the chromosomal DNA of all vertebrates tested, and its expression was found to be strongly correlated with tumorigenicity." Id., pages 2-3. The

specification discloses the full-length MN cDNA sequence. See Figure 15 and SEQ ID NO:5.

The specification discloses that MN was found to be expressed in a variety of tumor cells but not in normal tissues, with the exception of stomach tissue. See id., pages 8-9. "MN antigen was found by immunohistochemical staining to be prevalent in tumor cells. . . . Thus, the MN gene is strongly correlated with tumorigenesis and is considered to be a putative oncogene." Id., page 9.

The specification discloses that "[a]ntisense nucleic acid sequences substantially complementary to mRNA transcribed from MN genes . . . can be used to reduce or prevent expression of the MN gene. . . . Such antisense nucleic acid sequences, preferably oligonucleotides, by hybridizing to the MN mRNA, particularly in the vicinity of the ribosome binding site and translation initiation point, inhibits [sic] translation of the mRNA. Thus, the use of such antisense nucleic acid sequences may be considered to be a form of cancer therapy." Pages 92-93.

The specification discloses that non-tumorigenic (CGL1) cells¹ that were transfected with full-length MN cDNA had increased proliferation rates and plating efficiency. See pages 64-65. By contrast, when MN-expressing tumorigenic (CGL3) cells² were transfected with an MN antisense construct, "the effect was the opposite of that of the CGL1 cells transfected with the 'sense'

¹ See page 121, line 8 ("non-tumorigenic hybrid clone CGL1").

² See page 121, lines 6-7 ("Detected was a 1.5 kb MN-specific mRNA only in two tumorigenic segregant clones--CGL3 and CGL4.").

construct. Whereas the transfected CGL1 cells formed colonies several times larger than the control CGL1, the transfected CGL3 cells formed colonies much smaller than the control CGL3 cells.” Page 65.

Finally, the specification provides a working example showing inhibition of MN expression in vitro using either of two antisense oligonucleotides complementary to parts of SEQ ID NO:5. See pages 118-120. The two oligonucleotides are referred to as ODN1 (SEQ ID NO:3) and ODN2 (SEQ ID NO:4). The specification discloses that cells treated with ODN1 showed a 40% decrease in MN expression, while cells treated with ODN2 showed a 25-35% decrease. See page 119.

Discussion

The claims are directed to methods of treating neoplastic disease or inhibiting growth of tumor cells, where the disease or tumor cell growth is associated with abnormal MN gene expression, by administering an MN antisense oligonucleotide that is complementary to SEQ ID NO:5. SEQ ID NO:5 is the 1522-base pair, full-length MN cDNA sequence. See the specification, page 27, lines 21-22.

The examiner acknowledged that the claims are “enabl[ed] for a method for inhibiting the growth of a HeLa cell expressing a MN protein in vitro, the method comprising administering a composition comprising SEQ ID NO:3 or SEQ ID NO:4 to the cell so as to inhibit the growth of the cell.” Examiner’s Answer, page 4. He also acknowledged that the specification provides adequate guidance to enable those skilled in the art to determine whether a particular

cancer is associated with abnormal MN expression. Id., page 25. He concluded, however, that the claims are not enabled throughout their full scope because the specification “does not reasonably provide enablement for methods of treating neoplastic diseases and/or pre-neoplastic disease associated with abnormal MN gene expression, and of inhibiting the growth of a cancer cell that expresses MN protein in vivo.” Id.

The examiner’s enablement analysis considered several of the Wands factors. See the Examiner’s Answer, pages 4-12. In particular, the examiner relied on the following findings:

- The nature of the invention was a “nucleic acid therapy method.” Examiner’s Answer, pages 5-6.
- “At the time of filing the art recognized antisense therapy as in its infancy and as highly unpredictable.” Id., page 6. More specifically, “[d]etermining an effective antisense sequence, and transferring the antisense sequence to adequate numbers of target cells in vivo and getting specific binding between the antisense sequence and the target mRNA in an amount sufficient to produce a beneficial effect in any animal remain[ed] unpredictable at the time the invention was made.” Id. The examiner cited several references discussing various problems remaining to be overcome in the field of antisense therapy. See id., pages 6-10.
- The breadth of the claims “encompasses a wide range of antisense sequences, oligo structures, vector types, or compositions employed as therapeutic agents in the claimed antisense therapy methods to treat a wide range of different types of cancer associated with MN expression, in any and/or all vertebrate animals including humans.” Id., page 10.
- The specification provides working examples showing in vitro inhibition of tumorigenic cell growth and inhibition of MN gene expression. Id., page 11. However, the specification does not “demonstrate a reasonable correlation between the in vitro data, i.e., in vi[tro] inhibition of proliferation of a cultured tumorigenic human cell line (CGL3 cells) by direct injection of plasmids

expressing the antisense nucleic acids molecules of SEQ ID NO:3 of SEQ ID NO:4, and the [claimed method].” Id., page 5.

- Finally, the examiner found that the specification “failed to address” many of the issues that have hampered development of antisense therapeutic methods, including “stability of antisense nucleic acids in an in vivo environment . . .; the ability of a chosen antisense nucleic acid to reach and enter the target cell in vivo; . . . and specificity of an administered nucleic acid . . . to generate a desired therapeutic effect.” Id., pages 11-12.

The examiner concluded that “the specification is non-enabling in view of the complex and unpredictabl[e] nature of the subject matter, the lack of description and working examples which are correlating to the full scope of the claimed subject matter, the lack of guidance provided as to the selection of essential combination of parameters which would result in an effective therapeutic composition, and the amount of undue experimentation required to practice the full scope of the claimed invention.” Examiner’s Answer, page 12.

Appellants argue that the examiner has not made out a prima facie case of nonenablement, for several reasons. Appellants argue that the claims are relatively narrow, since the claims are limited to antisense sequences that are complementary to part of SEQ ID NO:5, and the specification provides an in vitro screening method that would enable those skilled in the art to select therapeutically useful antisense oligonucleotides. See the Appeal Brief, pages 24-25.

Appellants also argue that methods of administering therapeutic oligonucleotides were known in the art, as were methods for determining appropriate dosages. See the Appeal Brief, pages 17-18. Appellants argue that

the references cited by the examiner focus on optimization of antisense therapy to the point that it would be ready for clinical application. This standard, Appellants argue, is higher than what is required for enablement. See the Appeal Brief, pages 26-27. Appellants point to the approval of clinical trials using antisense oligonucleotides as evidence of enablement. See id., pages 29-30.

In support of each of the above arguments, Appellants cite declaratory evidence they submitted during prosecution. See the declaration submitted under 37 CFR § 1.132 by Dieter Cotter Gruenert (Paper No. 27, filed July 17, 1997), Appendix II to the Appeal Brief. The examiner disputes the probative value of the declaration, because “[s]ections 3, 4, 5, 6, and 8 as to the in vitro data . . . do not provide factual evidence to indicate that antisense nucleic acid therapy to treat all tumor bearing vertebrate animals . . . is reasonabl[y] predictive at the time the invention was made, nor do the sections provide factual evidence to demonstrate an extrapolation from the guidance and/or in vitro data disclosed in the as-filed application to the entire scope of the claimed invention.” Examiner’s Answer, pages 24-25.

“When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the

applicant to provide suitable proofs indicating that the specification is indeed enabling.” In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

“[E]nablement requires that the specification teach those in the art to make and use the invention without ‘undue experimentation.’ That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is ‘undue.’” In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (citation omitted, emphasis in original). “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Those considerations, see id., are well known; we need not repeat them here.

In this case, we agree with Appellants that the examiner has not shown that undue experimentation would have been required to practice the claimed method. The examiner’s concerns, and the evidence cited in support of the rejection, are mainly directed to sources of unpredictability and experimentation involved in antisense therapy in general, rather than the claimed method in particular. Granted, the examiner’s references show that (at least as of 1992) antisense therapy techniques, as a group, required further experimentation before they would be ready for clinical application. This showing, however, is not enough to support a rejection of the instant claims for nonenablement.

First, we agree with Appellants that a therapeutic method need not be ready for clinical application in order to be enabled. See In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995): “Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.”³ The references cited by the examiner seem to focus on the clinical application of antisense therapeutics. For example, the examiner cited Stull’s statement that “nucleic acid drugs must overcome several formidable obstacles before they can be widely used as therapeutics.” Examiner’s Answer, page 9. The examiner also cited Wagner as providing “evidence that antisense was . . . unpredictable at the time the invention was made.” Examiner’s Answer, page 9.⁴

While the references cited by the examiner provide evidence that antisense therapy, in general, was not ready for broad clinical application in the early 1990s, such evidence is not enough to show nonenablement. What is needed is evidence or sound scientific reasoning that undue experimentation would have been required to carry out the claimed methods. The claims are

³ Although the Brana court referred to “usefulness,” the rejection on appeal was based on 35 U.S.C. § 112, first paragraph. See 51 F.3d at 1564, 34 USPQ2d at 1439.

⁴ The examiner appears to have evaluated the enablement of the claims as of 1992, based on the filing date of the grandparent application of the present application. However, according to Appellants, the present application is a continuation-in-part of 08/188,093, filed Dec. 30, 1993, which was a continuation-in-part of 07/964,589, filed Oct. 21, 1992. Since the present application does not have the same disclosure as the earlier-filed applications, it is not necessarily entitled to § 120 benefit based on those earlier applications. However, the claims have not been rejected over intervening art, so we need not consider whether the instant claims are entitled to § 120 benefit. We will limit our analysis to whether the claims on appeal would have been enabled by the disclosure of the present application, in light of the state of the art as of this application’s 1994

variously directed to methods of “treating neoplastic disease and/or pre-neoplastic disease”, “inhibiting growth of a vertebrate cancer cell”, or “inhibiting the expression of a MN gene.” Thus, the claims at least encompass methods that require some degree of therapeutically beneficial effect. That standard, however, is more lenient than what is required for clinical application. See, e.g., Brana, 51 F.3d at 1568, 34 USPQ2d at 1442 (“On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical trials. . . . Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug . . . as well as its potential efficacy under different dosage regimens.”).

In this case, we have no fact-based explanation from the examiner focused on the claimed methods, as opposed to antisense therapy as a general field, to establish that the instant claims are nonenabled. In addition, it is well-established that the amount of experimentation that is considered “undue” varies from one field to another. See, e.g., Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (factors relating to undue experimentation include quantity of experimentation necessary, nature of the invention, and relative skill of those in the art).

filing date. Cf. Reiffin v. Microsoft Corp., 214 F.3d 1342, 1346, 54 USPQ2d 1915, 1917-18 (Fed. Cir. 2000).

In this case, the evidence shows that the FDA had approved several clinical trials of antisense drugs by 1994. For example, Reynolds disclosed that “the first approval from the Food and Drug Administration to test an antisense drug on patients” came in January 1992. See page 288, left-hand column. Wu-Pong reported that, in 1994, “several ON [oligonucleotide] drug candidates are currently being tested in clinical trials.” Page 110 (citing Alper, “Oligonucleotides Surge into Clinical Trials,” Bio/Technology, Vol. 11, p. 1225 (1993)). Wagner, also in 1994, stated that “[c]linical trials are now in progress to evaluate the therapeutic potential of antisense ODNs [oligodeoxynucleotides] in several human diseases, including myelogenous leukaemia, and infection by human immunodeficiency virus-1, cytomegalovirus (CMV) and human papillomavirus.” Page 333, left-hand column (citing references published in 1993 and 1994).

The approval by the FDA of clinical trials before and contemporaneous with the filing date of the instant application provides evidence that those skilled in the art of antisense methods regularly applied therapeutic techniques to human patients, despite the problems remaining to be overcome before the techniques could be widely applied clinically. Thus, the antisense protocols cited by Reynolds, Wu-Pong, and Wagner provide evidence that those practicing antisense techniques would not have considered the obstacles cited by the examiner to be a barrier to applying antisense therapies in human patients, and therefore, that those obstacles would not have been considered to be a source of undue experimentation in this field. There is no evidence in the record that the claimed antisense-based methods would have been likely to involve excessive

experimentation when considered relative to other antisense-based therapeutic methods.

Finally, we must also disagree with the examiner concerning the probative value of the Gruenert declaration. Dr. Gruenert declared that the in vitro results provided in the specification were reasonably predictive of in vivo efficacy. See ¶¶ 3-5. Dr. Gruenert also declared that the published literature at the time of filing would have supported an expectation of success in using MN antisense oligonucleotides to inhibit MN gene expression in vivo. See ¶ 6. Finally, Dr. Gruenert declared that the screening procedure disclosed in the specification, together with the published literature at the time of filing, would have enabled those skilled in the art to identify therapeutically useful oligonucleotides. See ¶¶ 7-8.

Of course, “Appellant’s opinion on the ultimate legal issue is not evidence in the case. . . . [However,] some weight ought to be given to a persuasively supported statement of one skilled in the art.” In re Lindell, 385 F.2d 453, 155 USPQ 521, 524 (CCPA 1967) (emphasis added). Here, the conclusions set out in the Gruenert declaration were well-reasoned and supported by evidence, either in the specification or in cited prior art references.

The lack of “factual evidence”, as the examiner put in, in addition to that provided in the specification, is not a fatal flaw in a Rule 132 declaration. Declaratory evidence can support patentability in a number of ways. In this case, the declaratory evidence was presented to show how the guidance provided by the specification, combined with the state of the art, would have been viewed by

a person of skill in the relevant field. The enablement requirement is determined, of course, from the perspective of those skilled in the art. See Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1335, 65 USPQ2d 1385, 1400 (Fed. Cir. 2003). (“[T]he [enablement] requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without ‘undue experimentation.’”).

The examiner appeared to start from the position that the claims were nonenabled, and then evaluate the declaration for whether it provided additional “factual evidence” in rebuttal. This approach is erroneous. “If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed.” In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986). See also In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976):

When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. . . . An earlier decision should not . . . be considered as set in concrete, and applicant’s rebuttal evidence then be evaluated only on its knockdown ability. Analytical fixation on an earlier decision can tend to provide that decision with an undeservedly broadened umbrella effect. Prima facie obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself.

While Hedges and Rinehart were addressed specifically to the issue of obviousness, the same evaluation applies to any patentability determination.

Even if a prima facie case is made out, when evidence is submitted in rebuttal, all

of the evidence of record must be considered in deciding whether the rejection is still viable. In this case, Appellants provided evidence showing that those skilled in the art would have viewed the guidance provided by the specification and the state of the art differently than the examiner viewed it. At that point, it was incumbent on the examiner, if he decided to maintain the rejection, to explain why a hypothetical "person of ordinary skill" was more likely to share his view of the evidence than that of Appellants' declarant. That was not done.

Thus, we conclude that the examiner has not shown that the amount of experimentation required to practice the instant claims would have been considered undue by those skilled in the art of antisense methods. The rejection for nonenablement is reversed.

Other Issues

As noted above (see footnote 4), we take no position on whether the instantly claimed invention would have been enabled by the disclosure in this application's parent or grandparent applications, combined with the state of the art in 1993 or 1992. Thus, if intervening prior art exists that would anticipate or render obvious the instant claims, the examiner should determine whether the instant claims are entitled to the benefit of the earlier-filed applications under 35 U.S.C. § 120. That is, the examiner should determine the effective filing date of the instant claims. If the effective filing date is later than any prior art that would anticipate the claims or render them obvious, a rejection under 35 U.S.C. § 102 or 35 U.S.C. § 103 may be appropriate.

Summary

The rejection for nonenablement is not supported by a preponderance of the evidence in the record. We therefore reverse the rejection under 35 U.S.C. § 112, first paragraph.

REVERSED

William F. Smith)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
Toni R. Scheiner)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
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