

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 34

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MARK D. CARMAN

Appeal No. 1997-2510
Application No. 07/868,539

ON BRIEF

Before WINTERS, SCHEINER, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL¹

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's rejection² of claims 1 and 3-11, which are all the claims pending in the application.

¹ We note that the "Request for Withdrawal as Attorney", received January 31, 2001 (Paper No. 32) was granted (Paper No. 33, mailed February 21, 2001). As set forth in Paper No. 33, "[n]o action will be taken in the appeal by the Board of Patent Appeals and Interferences for at least 30 days from the date of this letter so that the applicant will have sufficient time to obtain other representation or take appropriate action." Since the mailing of Paper No. 33, no further communication was received from appellant, or appellant's representative.

² We note that this appeal is from the examiner's non-Final Rejection (Paper No. 24, mailed June 15, 1995), of claims 1 and 3-11, which were "twice rejected" at the time the Notice of Appeal was filed. See 37 CFR § 1.191(a).

Claims 1 and 6 are illustrative of the subject matter on appeal and are reproduced below:

1. A method of inhibiting replication of a virus in an infected cell in vivo, comprising
selecting a DNA fragment having (i) a first region having 6-30 bases whose sequence corresponds to a sequence of DNA recognized by a viral-specific transcription factor, (ii) a second region having a sequence of nucleotides complementary to said first region, when said first and second regions are positioned in an anti-parallel configuration, and (iii) joining said first and said second regions in a 5' to 3' direction, a tetranucleotide sequence $X_1X_2X_3X_4$, where X_1 is U or T, and X_2 is U, T, G, A or C, and X_3 is C, and X_4 is G (SEQ ID NO: 14); or X_1 is G, and X_2 is U, T, G, A or C, and X_3 is G or A, and X_4 is A (SEQ ID NO: 15); or X_1 is C, and X_2 is U or T, and X_3 is U or T, and X_4 is G (SEQ ID NO: 16), and
introducing the fragment into the cell in an amount sufficient to inhibit replication of the virus in the cell.
6. A pharmaceutical composition for treating a virus infection, comprising a pharmaceutical excipient containing a DNA fragment having (i) a first region having a 5' terminus and a 3' terminus, said region having 6-30 bases whose sequence corresponds to a sequence of DNA recognized by a viral-specific transcription factor, (ii) a second region having a 5' terminus and a 3' terminus, said region having a sequence of nucleotides complementary to said first region when said first and second regions are positioned in an anti-parallel configuration, and (iii) a covalent link between the 5' terminus of one region and the 3' terminus of the other region.

The references relied upon by the examiner are:

Kaji	4,689,320	Aug. 25, 1987
Summerton et al. (Summerton)	5,142,047	Aug. 25, 1992
Inouye	5,208,149	May 4, 1993

Metzler, "Biochemistry: The Chemical Reactions of Living Cells," Academic Press Inc., p. 103 (1977)

Snedecor et al. (Snedecor), "Statistical Methods," Iowa State University Press/Ames, 8th Edition, pp. 10-13, 26-37 (1989)

Uhlmann et al. (Uhlmann), "Antisense Oligonucleotides : A New Therapeutic Principle," Chemical Reviews, Vol. 90, No. 4, pp. 544-579 (1990)

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Sakata et al. (Sakata), "Studies on the structure and stabilizing factor of the CUUCGG hairpin RNA using chemically synthesized oligonucleotides," Nucleic Acids Research, Vol. 18, No. 13, pp. 3831-3839 (1990)

Mitsuya et al. (Mitsuya), "Molecular Targets for AIDS Therapy," Science, Vol. 249, pp.1533-1544 (1990)

Bielinska et al. (Bielinska), "Regulation of Gene Expression with Double-Stranded Phosphorothioate Oligonucleotides," Science, Vol. 250, pp. 997-1000 (1990)

Vickers et al. (Vickers), "Inhibition of HIV-LTR gene expression by oligonucleotides targeted to the TAR element," Nucleic Acids Research, Vol. 19, No. 12, pp. 3359-3368 (1991)

Everett et al. (Everett), "Purification of the DNA binding domain of herpes simplex virus type 1 immediate-early protein Vmw175 as a homodimer and extensive mutagenesis of its DNA recognition site," Nucleic Acids Research, Vol. 19, No. 18, pp. 4901-4908 (1991)

Stein et al. (Stein), "Antisense Oligonucleotides as Therapeutic Agents – Is the Bullet Really Magical?," Science, Vol. 261, pp. 1004-1012 (1993)

Antisense Update: Keep Your Chin Up - - Other Forms of Antisense: Lack of Obvious Progress, Genis Report – Rx, Vol. 2, No. 4 (Genesis Group Associates, Inc.) (1993)

Wagner, "Gene inhibition using antisense oligodeoxynucleotides," Nature, Vol. 372, pp. 333-335 (1994)

Conference Coverage (ICAAC) Antisense Drug Stumbles in Early Trial, Infectious Disease Weekly (Charles W Henderson) (1995)

Gura, "Antisense Has Growing Pains," Science, Vol. 270, pp. 575-577 (1995)

Stull et al. (Stull), "Antigene, Ribozyme and Aptamer Nucleic Acid Drugs: Progress and Prospects," Pharmaceutical Research, Vol. 12, No. 4, pp. 465-483 (1995)

GROUND OF REJECTION

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Claims 1 and 3-11 stand rejected under 35 U.S.C. § 112, first paragraph, as specification does not contain (i) an adequate written description and (ii) a sufficient disclosure to support or enable the scope of the claimed invention.

Claims 1 and 3-11 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

Claims 1, 3 and 6-8 stand rejected under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye.

Claims 1, 3 and 6-8 stand rejected under 35 U.S.C. § 103 as obvious over Bielinska, in view of Sakata, Uhlmann and Inouye.

Claims 5 and 11 stand rejected under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Kaji and Everett.

Claim 10 stands rejected under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Mitsuya.

Claims 4 and 9 stand rejected under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Summerton.

We reverse the rejections under 35 U.S.C. §§ 112, second paragraph and 103. We vacate the rejection under 35 U.S.C. § 112, first paragraph and remand the application to the examiner for further consideration.

DISCUSSION

In reaching our decision in this appeal, we considered appellant's specification and claims, in addition to the respective positions articulated by the appellant and the examiner. We make reference to the examiner's Answer³, and the examiner's Supplemental Answer⁴ in response to appellant's Reply Brief⁵, for the examiner's reasoning in support of the rejections. We further reference appellant's Brief⁶, and appellant's Reply Brief for appellant's arguments in favor of patentability.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

For the reasons set forth below, we have determined that the rejection under 35 U.S.C. § 112, first paragraph is not based upon the correct legal standards. Accordingly we vacate⁷ the rejection under 35 U.S.C. § 112, first paragraph, and remand the application to the examiner to consider the following issues and take appropriate action.

I. The severability of the "written description" provision from the enablement provision of 35 U.S.C. §112, first paragraph:

Appellant explains (Brief, page 20) "[t]he written description requirement is separate and distinct from the enablement requirement." See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (CAFC 1991). However, the examiner argues (Answer, page 18) "[w]hile

³ Paper No. 29, mailed August 8, 1996.

⁴ Paper No. 31, mailed December 10, 1996.

⁵ Paper No. 30, received October 15, 1996.

⁶ Paper No. 28, received May 17, 1996.

appellant would argue that written description is separate from enablement, when there is inadequate written description, there is no enablement (i.e., what is not described is not enabled).”

Throughout the body of his rejection and response to appellant’s arguments, the examiner commingles the written description and enablement provisions of 35 U.S.C. § 112, first paragraph. At no point, on this record, does the examiner clearly address the issue of written description, separately from the issue of enablement.

The written description provision is separate and distinct from the enablement requirement. Vas-Cath, 935 F.2d at 1560, 19 USPQ2d at 1114. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116. The enablement requirement of 35 U.S.C. § 112, first paragraph, requires that the patent specification enable “those skilled in the art to make and use the full scope of the claimed invention without ‘undue experimentation.’” Genentech, Inc. v. Novo Nordisk. A/S, 108 F.3d at 1365, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)).

⁷ Lest there be any misunderstanding, the term “vacate” in this context means to set aside or to void. When the Board vacates an examiner’s rejection, the rejection is set aside and no longer exists.

By addressing the written description and enablement provisions of 35 U.S.C. § 112, first paragraph together, the examiner failed to focus on the requirements of either provision. Thus, the rejection is not susceptible to a meaningful review. Accordingly, we vacate the examiner's rejection and remand the application. Upon receipt of the application, the examiner should step back and reconsider the issue of written description separately from the issue of enablement. If, the examiner believes that a rejection under the written description provision or the enablement provision is necessary, the examiner should issue an appropriate office action, that clearly sets forth the factual basis for the rejection. In the event the examiner finds that a rejection under the written description provision and the enablement provision is required, the examiner should issue an appropriate Office Action, separately addressing, and clearly setting forth the factual basis for each rejection.

While we take no position on the merits of the examiner's rejection. We offer the following guidance, and make the following observations, to assist the examiner's in his reconsideration of this record.

A. Written Description:

As set forth in Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) the written description "inquiry is a factual one and must be assessed on a case-by-case basis." Furthermore, "the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention

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defined by the claims.” In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). As set forth in Wertheim, 541 F.2d at 262, 191 USPQ at 96:

The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material. In re Smith, 481 F.2d 910, 178 USPQ 620 (CCPA 1973), and cases cited therein. It is not necessary that the application describe the claim limitations exactly, In re Lukach, [442 F.2d 967, 169 USPQ 795 (1971)]... but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations. In re Smythe, 480 F.2d 1376, 1382, 178 USPQ 279, 284 (CCPA 1973).

The primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.

B. Enablement:

In considering the issue of enablement, we note that in order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371-72, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999). However, “nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples.” In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). As set forth in In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993):

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.

With regard to the examiner's burden of setting forth a reasonable explanation as to why he believes the specification does not enable the claimed invention, we note that determining whether the disclosure is enabling, is a legal conclusion based on several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

We also recommend that the examiner review Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999). Therein, the court provided a model analysis of enablement issues and illustrated the type of fact finding which is needed before one is in a proper position to determine whether a given claim is enabled or non-enabled.

II. Utility:

The examiner's statement of the rejection in the Answer refers to both "written description" and "enablement". The statement of this rejection in the examiner's June 15, 1995 Office Action (page 2) also referred to "written description" and "enablement". However, in developing this rejection in the June 15, 1995 Office Action, the examiner states "[t]he mention at page 14, lines 1-5 of various routes of administration is insufficient written description, enablement, and best mode to show efficacy" [emphasis added]. Furthermore, in responding to appellant's argument (Brief, pages 23-24) regarding the best mode issue, the examiner argues (Answer, page 24), "the present rejection is not predicated upon best mode. The comments are, thus, not persuasive nor is there any cure for the common cold, a viral based disease" [emphasis added].

It appears from these statements that the examiner is concerned about the utility of the claimed invention. However, absent these spurious comments by the examiner, this record fails to develop this issue. It is unclear to this Merits Panel, why the examiner would be compelled to address "efficacy" or comment on a "cure for the common cold" if the utility of the claimed invention is not at issue. Upon further prosecution, the examiner should clarify this issue.

III. New Matter:

To further confuse this record, at page 19 of the Answer, the examiner argues “the present rejection is not for new matter but that the claims are rejected because the written description fails to meet the written description requirement.” However, in the very next two sentences (id.) the examiner states “[t]he instant claims on appeal are amended claims, not originally filed claims. It is the written description which is inadequate and which also does not enable the claims.”

It is unclear, why after affirmatively stating that the rejection is “not for new matter” the examiner is compelled to point out that the “claims on appeal are amended claims, not originally filed claims.” Upon further prosecution, the examiner should clarify this issue.

IV. Toxic Side Effects:

We note the examiner’s reference (Answer, 16) to Gura arguing, “that there [are] further unsolved problems with using are [sic] oligonucleotides as in unforeseen difficulties such as toxic side effects including increased blood pressure and decreased heart rate.”

With regard to examiner’s concern about toxic side effects, it appears that the examiner is confusing the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. See Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) (“Testing for the full safety and

effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA).”). Upon further prosecution, the examiner should clarify this issue.

V. Antisense References:

The examiner refers (Answer, pages 16-17) to the Infectious Disease Weekly, the Genesis Report-RX, Gura, Wagner, and Stull to support his arguments. The examiner, however, has failed to explain the nexus between these references, which discuss antisense technology, and the claimed invention. In this regard, we note appellant’s statement (Brief, page 5) that “the [m]olecules constructed according to the claimed method of the present invention are NOT designed to interact (i.e., specifically hybridize) with the DNA and/or RNA of the host or virus.” Upon further prosecution, the examiner should address appellant’s comment, and explain the nexus between the claimed invention and any reference relied upon by the examiner.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

As set forth in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991):

The statute requires that “[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.” A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must “reasonably apprise those skilled in the art” as to their scope and be “as precise as the subject matter permits.”).

We note the examiner's reference to In re Zletz, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). According to the examiner (Answer, page 5) Zletz stands for the proposition that "there is no reason to read into the claim(s) limitations of the specification...." We agree with the examiner (id.) that an "essential purpose of patent ... examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process." Zletz, 893 F.2d at 321-22, 13 USPQ2d at 1322. We note that claim language must be analyzed "not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

Claims 1 and 6:

According to the examiner (Answer, page 4) "claims 1 and 6 are unclear as to what is meant to be included or excluded by recitation of 'whose sequence corresponds to a sequence of DNA recognized by a viral specific transcription factor'...." The examiner reasons (id.):

The DNA is one single strand of DNA even where it is argued that the DNA in claim 1 is indicated as joined by traditional 5' to 3' phosphodiester bonds. Joining results in a single piece of DNA Thus, the claim is indefinite as there are no multiple fragments, but only one fragment and the metes and bounds of the first and second regions coincide and include the X₁ to X₄ [region]."

The examiner's statement of the rejection is somewhat confusing. Initially, the examiner finds the term "corresponds" unclear in the phrase "whose sequence corresponds to a sequence of DNA recognized by a viral specific transcription factor." Then, in further developing the statement of the rejection, the examiner appears to be confused about appellant's use of the term "region" arguing that "there are no multiple fragments."

We agree with appellant (Brief, page 26) "that one of skill in the art would have no difficulty in interpreting ... [the claims] in light of the specification." With regard to the examiner's argument that "there are no multiple fragments", we agree. There are no multiple fragments. Instead, the claims comprise a DNA fragment. This DNA fragment has two regions that are joined by "a tetranucleotide sequence" of defined structure in claim 1; or a "covalent link" in claim 6. In our opinion, when the claims are read as a whole, a person of ordinary skill in the art would not find the claims vague or indefinite.

With regard to the term "comprising", appellants direct (Brief, page 25) "the [e]xaminer's attention to the table in Figure 4, which shows exemplary sequences recognized by transcription factors from a number of viruses." The examiner misconstrues appellant's (Answer, page 25) reference to the table in Figure 4, as an attempt by appellant to read the limitations of the figure into the claim. We recognize as set forth in Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1186, 48 USPQ2d 1001, 1005 (Fed. Cir. 1998):

[T]hat there is sometimes a fine line between reading a claim in light of the specification, and reading a limitation into the claim from

the specification. See, e.g., 1 Donald S. Chisum, Chisum on Patents Section 3.02 [1] & n.12 (rel. Dec. 1996) ("The line between interpreting claim language in light of the specification and reading a limitation from the specification into the claim is a fine one.").

However, in our opinion, by reference to Figure 4, appellant is merely providing exemplary sequences that "correspond to a sequence of DNA recognized by a viral-specific transcription factor" (see Specification, page 7, description of Figure 4). Therefore, in our opinion, when the claims are read in light of the specification, a person of ordinary skill in the art would reasonably understand what is intended by the phrase "corresponds to a sequence of DNA recognized by a viral-specific transcription factor".

Claim 7:

According to the examiner (Answer, bridging paragraph, pages 4-5):

In claim 7 ... the "one region" (second to last line) is indefinite as to the end where X_1 is covalently attached is the 3' end of X_1 ... attached to the ... 3' end of the "one region" (is it the first region or the second region that is referred to as the 'one region'? Similarly, the [sic] it is not clear as to whether the "and X_4 is covalently attached refers to the 5' end of X_4 ; attached to the 5' end of the "other region". Is it the first region or the second region that is referred to as the "other region"?

In response, appellant argues (Brief, page 26) that "[t]he claim refers to two regions of DNA which are joined by a linker in the 5' to 3' direction. It does not matter which of the two regions is first ... and which is second." Appellant further argues (id.) "one of skill in the art could make the determination that the

'other' region is the one that was not covalently attached to X₁." We agree with appellant.

Accordingly, we reverse the rejection of claims 1 and 3-11 under 35 U.S.C. § 112, second paragraph.

THE REJECTIONS UNDER 35 U.S.C. § 103:

The rejection of claims 1, 3 and 6-8 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye.

Initially, we note that the examiner's statement of the rejection (Answer, page 7) is something less than a coherent thought. According to the examiner (Answer, page 7) Vickers:

disclose a DNA hairpin structure where the nucleotides making up the loop are shown in figure 3 (note the lengths of 28, 18, and 26 bases). The DNA is disclosed as targeted to the "TAR" element where the disclosed loop contains bases such as A, U, C, and G ... and is an oligonucleotide targeted to a viral transcription factor that inhibited gene expression and HIV replication.... [Vickers] put the constructs into cells and indicated that (page 3365) that [sic] the "results demonstrate that antisense oligonucleotide targeted to the bulge and loop regions of TAR are capable of binding and disrupting the native TAR structure at pharmacological reasonable concentrations ...["].

The examiner finds (*id.*) Sakata "disclose oligonucleotides with hairpin loop (note the UUCG, figure 1 and the 13+ bases among others) structures formed with a single strand of DNA (and have an unusually high T_m and thermal stability) as do appellant's claimed compositions and [the] compositions recited in the [claimed] method of inhibiting viral replication." The examiner further explains (Answer, page 29):

The Sakata et al. reference indicated the state-of-the-art, and, what is obvious for one of ordinary skill in the art to do with oligonucleotides with hairpin loops.... The reference indicates that these structures are formed of single stranded DNA and have unusually high T_m and thermal stability and indicate what kinds of bases in the loop effect stability in conjunction with the stem part of the construct.

Therefore the examiner concludes (Answer, page 7) to obtain high T_m and thermal stability it would have been obvious to substitute the “UUCG” sequence taught by Sakata into the loop of Vickers.

The examiner relies on Metzler (Answer, page 29) to demonstrate that calculating energy of formation of stem-loop structures was within the skill of a person of ordinary skill in the art. In addition, the examiner identifies (Answer, page 7) a number of teachings in Uhlmann “improve transport and hybridization (page 558)”, “interactive groups (page 573+) for the target nucleic acids”, and “have been conjugated to proteins (page 560 and 561) via various linkers such as mercapto groups.” However, it is not until the examiner responds to appellant’s arguments (Answer, bridging paragraph, pages 29-30) that the examiner’s reliance on Uhlmann is explained:

Uhlmann et al. disclosed attachment of group specific reactive moieties (see at least page 550) to improve transport and hybridization (page 558). From the teaching in the reference, one of ordinary skill in the art would have had and known of interactive groups (page 573+) for the target nucleic acids and have conjugated the oligonucleotides and proteins (page 560 and 561) via various linkers such as mercapto groups.

Finally, the examiner relies on Inouye (id.) for the disclosure of “constructs that form a stem and loop structure....”

We recognize appellant's argument (Brief, page 14) that "Vickers suggest [page 3368, first column, last sentence] that the oligonucleotide target, or TAR element, acts as a translational rather than a transcriptional factor." We note however, that the claims merely require that the DNA "sequence corresponds to a sequence of DNA recognized by a viral-specific transcription factor." As explained by the examiner, see supra, Vickers teach (figure 3, and Table 1) "antisense oligonucleotides directed against the HIV TAR element." While we agree with appellant that Vickers suggests that TAR may act as a translational repressor, Vickers teaches (bridging paragraph, page 3367, column 2 – page 3378, column 1) "tat functions at the level of transcription by binding TAR...." Thus, Vickers teaches an antisense oligonucleotide complimentary to the HIV TAR element which is recognized by the viral-specific transcription factor, tat.

However, we further note, that according to the claimed invention (see e.g., claims 1 and 6), the DNA fragment has a first region having 6-30 bases whose sequence corresponds to a sequence of DNA recognized by a viral-specific transcription factor, and a second region having a sequence of nucleotides that is complementary to said first region when the two sequences are positioned in an anti-parallel configuration. While Vickers teaches a DNA sequence that corresponds to a sequence of DNA recognized by a viral-specific transcription factor, Vickers fails to teach a DNA fragment whose first 6-30 base

region is complementary to a second region, when the two regions are positioned in an anti-parallel configuration, as required by the claimed invention.

In addition, there is nothing in Vickers that suggests the antisense oligonucleotides, set forth in Table 1, are capable of forming any type of secondary structure. In contrast, as set forth in appellant's specification (page 9) "[t]he complementary strands forming the majority of the DNA fragment are hydrogen bonded as indicated by the dotted lines to form the structure shown" in Figures 1-3. Nevertheless, to the extent that Vickers' sequences would form a stem-loop structure, each of the antisense oligonucleotides illustrated in Table 1 of Vickers, contains mismatched sequences. We note, the "UCU" "buldge" on the left side of the constructs in Figure 3 of Vickers. This "buldge" is reproduced as "AGA" in Vickers' antisense oligonucleotides. See for example, the sequences corresponding to compound # 1308, 1307 and 1972, illustrated in Table 1, page 3365 of Vickers. According, to the claimed invention, the second region is complementary to the first region, therefore there are no mismatched sequences in the stem portion (e.g., the first and second region) of appellant's claimed DNA fragment.

We are also not persuaded by the examiner's arguments concerning the suggestion to combine Vickers with Sakata. According to the examiner (Answer, page 29) Sakata illustrates the "state-of-the art, and, what is obvious for one of

ordinary skill in the art to do with oligonucleotides with hairpin loops". Sakata teach "[s]tudies on the structure and stabilizing factor of the CUUCGGG hairpin RNA." See title. While Sakata teach that "the 2-amino group of guanosine in the loop (9G) stabilize the CUUCGG hairpin which is known to have an unusually high T_m" (see Abstract), the examiner fails to identify some reason or suggestion as to why a person of ordinary skill in the art would substitute this CUUCGG sequence into Vickers' antisense oligonucleotides.

The examiner fails to explain why a person of ordinary skill in the art would want to modify Vickers to produce a hairpin with an unusually high T_m. The examiner also fails to explain why one of ordinary skill in the art would expect the six nucleotides of Sakata to maintain their unusually high T_m in the context of the construct taught by Vickers. We remind the examiner, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

The Metzler, Uhlmann and Inouye references fail to make up for the deficiencies in the combination of Vickers and Sakata. We note, the examiner's reference to the claims of Inouye. Inouye does not teach a DNA fragment according to the claimed invention wherein a first region whose sequence

corresponds to a sequence of DNA recognized by a viral-specific transcription factor is linked to a second region having a sequence of nucleotides complementary to said first region when the first and second regions are positioned in an anti-parallel orientation. In contrast, claim 1 of Inouye is drawn to a stem-loop structure (claim 1, part b) flanked on either side by a transcriptional promoter segment (claim 1, part a) and a gene segment (claim 1, part c). Accordingly, the sequence of DNA recognized by a viral-specific transcription factor (e.g. "transcriptional promoter segment") is not part of the stem-loop structure, as is required by the instant claims.

To establish a prima facie case of obviousness, there must be more than the demonstrated existence of all of the components of the claimed subject matter. There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 678-79, 7 USPQ2d 1315, 1318 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985). On the record before us, we find no reasonable suggestion for combining the teachings of the references relied upon by the examiner in a manner which

would have reasonably led one of ordinary skill in this art to arrive at the claimed invention.

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). Therefore, on these facts, it is our opinion that the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. If the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Accordingly, we reverse the examiner's rejection of claims 1, 3 and 6-8 under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye.

The rejection of claims 1, 3 and 6-8 over Bielinska, in view of Sakata, Uhlmann and Inouye:

According to the examiner (Answer, page 8) Bielinska:

disclose double stranded oligonucleotide DNA that resulted in >90% reduction in gene expression (Epstein-Barr virus) and over 80% inhibition for HIV-CAT.... Insofar as oligonucleotides are disclosed, it would have, nevertheless, been obvious to one of ordinary skill in the art that where Sakata et al. disclosed double stranded polynucleotides with greater thermal stability when they are connected via a hairpin loop ... to have connected the double stranded oligonucleotides disclosed in the Bielinska et al. reference with loop structures disclosed in the Sakata et al. reference for increased stability when used in vivo."

The examiner further finds (id.) that Uhlmann teaches “modifications to the bases and base linkages ... increase stability and serum half-life ... [in addition to] oligonucleotide modification to add interactive groups ... and that target sequences ... include regions of the DNA where the regulatory DNA binding proteins normally bind....” In addition, the examiner finds (Answer, page 9) that “Inouye discloses and claims pharmaceutical compositions containing polynucleotide constructs with a stem ... and a loop where the stem-loop structure is targeted to a regulator (see for example the Inouye patent claims 1, 15 and 16).”

Appellant argues (Brief, page 15) that Bielinska does not suggest that claimed DNA fragment that includes a sequence of DNA recognized by a viral-specific transcription factor, and a covalent link between the complimentary strands of DNA. In addition, appellant argues (id.) “the [e]xaminer has not presented references suggesting that such an oligonucleotide may be effective in inhibiting replication of the virus.”

In response, the examiner argues (Answer, page 30) this “comment is not persuasive in view of the combined cited references where Vickers et al. do indicate expectation and suggestion of inhibition of viral replication... The

combined references of Vickers et al., Bielinska et al., Sakata et al., Uhlmann et al., and Inouye” Vickers, however, is not part of this rejection.

With regard to the modification of Bielinska with Sakata, absent appellant’s disclosure, the examiner has not identified any portion of the references relied upon that suggests to a person of ordinary skill in the art to remove the loop from Sakata’s stem-loop construct and place it on the construct of Bielinska.

As set forth in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. ... Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one “to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.”

...
Most if not all inventions arise from a combination of old elements. ... Thus, every element of a claimed invention may often be found in the prior art. ... However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. ... Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. [citations omitted]

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In other words, “there still must be evidence that ‘a skilled artisan, . . . with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.” Ecolochem Inc. v. Southern California Edison, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075-76 (Fed. Cir. 2000).

In addition, we are not persuaded by the examiner’s argument that a person of ordinary skill in the art would make such a modification to increase the stability of the molecule in vivo. The examiner fails to explain why one of ordinary skill in the art would expect the six nucleotides of Sakata to maintain their unusually high T_m in the context of the construct taught by Bielinska, without interfering with the function of the Bielinska construct. As discussed, supra, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442. At best, the examiner has established an “obvious to try” situation. “Obvious to try”, however, is not the standard of obviousness under 35 U.S.C. § 103. In re O’Farrell, 858 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

On the record before us, we find no reasonable suggestion for combining the teachings of the references relied upon by the examiner in a manner which would have reasonably led one of ordinary skill in this art to arrive at the claimed

invention. 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). Therefore, on these facts, it is our opinion that the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. If the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Accordingly we reverse the rejection of claims 1, 3 and 6-8 under 35 U.S.C. § 103 as obvious over Bielinska, in view of Sakata, Uhlmann and Inouye.

The rejection of claims 5 and 11 over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Kaji and Everett.

According to the examiner (Answer, page 9) Kaji discloses using DNA coding for herpes virus Vmw 175 protein where Everett et al. disclose sequences to which Vmw 175 binds....” The examiner finds (id.) “[t]he DNA disclosed in the Everett et al. reference has a known antiparallel strand deducible from the disclosed sequence.” However, while the examiner directs our attention to page 4901 and to Table 1 of Everett, the examiner fails to identify which sequence he is relying on to teach the “known antiparallel strand[s]”. The best we can surmise is the examiner is referring to the schematic representation (see Everett, Figure 1) of the structure of the HSV-1 genome that

illustrates the two IE-3 regions oriented in opposite directions. Notwithstanding the examiner's failure to clearly identify the evidence supporting his argument, the examiner finds (Answer, page 10) that "[h]ere, one of ordinary skill in the art would have found it obvious to decrease Vmw 175 binding by using the DNA with the sequence of 5' ... NATCGTCCACACGGNN NNCCGTGTAAGGACGATN ... 3' to bind to the Vmw 175 protein...."

Appellant argues (Brief, pages 16-17) "Kaji teaches the use of single-stranded oligonucleotides that bind to viral mRNA ... [t]he method would not work if double-stranded DNA were employed." As appellant emphasizes (id.), in contrast to the claimed invention, Kaji repeatedly states that compositions effective to inhibit viral replication are single stranded. We remind the examiner, that in determining whether the claimed invention is obvious, a prior art reference must be read as a whole and consideration must be given where the reference teaches away, as it does in the case of Kaji, from the claimed invention. Akzo N.V., Aramide Maatschappij v.o.f. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1481, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986).

With regard to Everett, appellant argues (Brief, bridging paragraph, pages 17-18) while "Everett teaches the nucleotide sequence requirements of a transcription factor protein Vmw175, Everett provides no motivation for synthesizing oligonucleotides containing self-complimentary regions...."

In response, the examiner argues (Answer, page 32) that “[o]ne of ordinary skill in the art would have found it obvious to decrease Vmw 175 expression using DNA (sequence 5’ ... NATCGTCCACACGGNN NNCCGTGTGGACGATN ... 3’) that interrupts the normal DNA binding to Vmw 175 protein by using DNA which is antiparallel to NATCGTCCACACGGNN bind to the HSV-1 DNA to inhibit expression” The examiner however, fails to identify any portion of Everett or Kaji, from which this statement of obviousness is derived.

On the record before us, we find no reasonable suggestion for combining the teachings of the references relied upon by the examiner in a manner that would have reasonably led one of ordinary skill in this art to arrive at the claimed invention. 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). Therefore, on these facts, it is our opinion that the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. If the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly we reverse the rejection of claims 5 and 11 under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Kaji and Everett.

The rejection of claim 10 over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Mitsuya:

According to the examiner (Answer, page 11) Mitsuya “disclose ... combinations of multiple antiviral drugs and indicate enhancing the efficacy of each drug in the combination ... while reducing the adverse reactions to the drugs....” Therefore, the examiner concludes (id.) “[i]t would ... have been obvious to one of ordinary skill in the art to combine the DNA therapy with that of other known antiviral drugs such as AZT.”

However, Mitsuya fails to make up for the deficiency in the combination of Vickers in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye. See supra.

Accordingly we reverse the rejection of claim 10 under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Mitsuya.

The rejection of claims 4 and 9 over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Summerton:

According to the examiner (Answer, page 12) “it would have been obvious to use halo-purine and/or halo-uridine analogs such as disclosed by Summerton et al. Summerton in the DNA because Summerton et al. disclose ... that the DNA is to inhibit and/or inactivate target polynucleotides such as disclosed in the combined cited references....”

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Summerton, however, fails to make up for the deficiency in the combination of Vickers in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye. See supra.

Accordingly we reverse the rejection of claims 4 and 9 under 35 U.S.C. § 103 as obvious over Vickers, in view of Sakata, Metzler, Uhlmann and Inouye; or Bielinska, in view of Sakata, Uhlmann and Inouye, further in view of Summerton.

REVERSED, VACATED and REMANDED

Sherman D. Winters)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
Toni R. Scheiner)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
)	
Donald E. Adams)	
Administrative Patent Judge)	

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