

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 49

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JANICE A. KOLBERG
and MICHAEL S. URDEA

Appeal No. 1997-2532
Application No. 08/427,569¹

ON BRIEF

Before WINTERS, SPIEGEL, and SCHEINER, Administrative Patent Judges.
SPIEGEL, 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 17 through 36, which are all of the claims pending in this application.

The claimed invention is directed to sandwich hybridization assays for detecting HTLV-1 (claims 31-33), probes (claims 17-30) and kits (claims 34-36) therefore. Two

¹ Application for patent filed April 24, 1995. According to appellants, this application is a continuation of application 08/130,150 filed September 29, 1993, now abandoned, which is a continuation of application 07/813,585 filed December 23, 1991, now abandoned.

types of probes are claimed, i.e., amplifier and capture probes. Each probe has a first segment, i.e., an oligonucleotide of defined nucleic acid sequence, which hybridizes to a complementary distinct, separate nucleic acid sequence of the HTLV-1, thereby "sandwiching" the HTLV-1 between the probes. The capture probe (claims 20-22) has a second segment of nucleic acids complementary to the nucleic acid sequence of a solid phase oligonucleotide which allows separation of the complex of the sandwiched HTLV-1 from unreacted assay components, while the amplifier probe (claims 17-19) has a second segment of nucleic acids complementary to a "connecting" oligonucleotide segment of a "multimer." Neither second segment is complementary to an HTLV-1 nucleic acid sequence. In addition to the "connecting" oligonucleotide, the multimer also contains multiple oligonucleotides which are complementary to a labeled oligonucleotide. Thus, hybridization between the amplifier probe and the multimer ultimately "amplifies" the amount of label attached to the sandwich HTLV-1 via hybridization between the multimer and the labeled oligonucleotide. Claims 23-26 and 27-30 are directed to sets of two or more amplifier probes having different first segments and sets of two or more capture probes having different first segments. The first segments of the amplifier and capture probes comprise sequences selected from SEQ ID NOs. 6-41 and SEQ ID NOs. 42-53, respectively.

Claims 23 and 31 are illustrative and read as follows:

23. A set of synthetic oligonucleotides useful as amplifier probes in a sandwich hybridization assay for HTLV-1, comprising at least two different oligonucleotide probes, wherein each oligonucleotide probe consists of:

a first segment having a minimum length of about 25 nucleotides and a maximum length of about 100 nucleotides which segment is at least 90% homologous to a segment of HTLV-1 nucleic acid, wherein said first segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS: 6-41; and

a second segment consisting of a nucleotide sequence which is at least 90% homologous to an oligonucleotide segment of a nucleic acid multimer wherein said second segment is not complementary to HTLV-1 nucleic acid;

and optionally one or more noncomplementary segments each consisting of a nucleotide sequence that is not complementary to HTLV-1 nucleic acid.

31. A solution sandwich hybridization assay for detecting the presence of HTLV-1 in a sample, comprising:

(a) contacting the sample with (i) amplifier probes comprising the set of synthetic oligonucleotides of claim 23 and (ii) a set of capture probe oligonucleotides wherein there is a molar excess of amplifier probes and of capture probes over analyte nucleic acid in the sample, wherein said set of capture probe oligonucleotides comprises at least two different oligonucleotides each of which consists of

a first segment having a minimum length of about 25 nucleotides and a maximum length of about 100 nucleotides which segment is at least 90% homologous to a segment of HTLV-1 nucleic acid, wherein said first segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS: 42-53; and

a second segment consisting of a nucleotide sequence which is at least 90% homologous to an oligonucleotide bound to a solid phase wherein said second segment is not complementary to HTLV-1 nucleic acid;

and optionally one or more noncomplementary segments each consisting of a nucleotide sequence that is not complementary to HTLV-1 nucleic acid;

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- (b) contacting the product of step (a) with said oligonucleotide bound to the solid phase;
- (c) thereafter separating materials not bound to the solid phase;
- (d) contacting the bound product of step (c) with a nucleic acid multimer, said multimer comprising at least one oligonucleotide segment that is at least 90% homologous to the second segment of the amplifier probe polynucleotide [sic, oligonucleotide] and a multiplicity of second oligonucleotide segments that are at least 90% homologous to a labeled oligonucleotide;
- (e) removing unbound multimer;
- (f) contacting the solid phase complex product of step (e) with the labeled oligonucleotide;
- (g) removing unbound labeled oligonucleotide; and
- (h) detecting the presence of label in the solid phase complex product of step (g) and, thereby, detecting the presence of virus in the sample.

The references relied on by the examiner are:

Hogan et al. (Hogan) (published International Application)	WO 88/03957	June 2, 1988
Urdea et al. (Urdea) (published International Application)	WO 89/03891	May 5, 1989

Seiki et al. (Seiki), "Human adult T-cell leukemia virus: Complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA," Proceedings of the National Academy of Sciences, USA, Vol. 80, pp. 3618-3622 (June 1983).

Stratagene 1988 Catalog, p. 39 (Stratagene).

Ratner et al. (Ratner), "Nucleotide Sequence Analysis of Isolates of Human T-Lymphotropic Virus Type I of Diverse Geographical Origins," AIDS Research and Human Retroviruses, Vol. 7, No. 11, pp. 923-941 (November 1991).

ISSUES²

² The examiner withdrew the final rejection of claims 17-36 under 35 U.S.C. § 112, first paragraph, as lacking enablement (see answer, para. bridging pp. 7-8).

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Claims 17-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner. Claims 34-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner and further in view of Stratagene. We REVERSE both rejections.

In reaching our decision in this appeal we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's answer (Paper No. 42, mailed November 26, 1996) for the examiner's reasoning in support of the rejection and to the appellants' brief (Paper No. 41, filed September 26, 1996) and to appellants' reply brief (Paper No. 43, filed January 24, 1997)³ for the appellants' arguments thereagainst.

OPINION

Urdea discloses a generic solution sandwich hybridization assay comprising (a) contacting a sample with (i) an amplifier probe having a first segment that is complementary to a first portion of a nucleic acid sequence of interest and a second segment that is complementary to a oligonucleotide unit of a nucleic acid multimer and (ii) a capture probe having a first segment that is complementary to a second, different portion

³ After initially denying entry of appellants' reply brief in a communication mailed February 25, 1997 (Paper No. 44), the examiner later entered the reply brief "[i]n view of the new rules for entry of reply briefs which went into effect December 1, 1997, which require the entry of reply briefs" (see communication mailed December 12, 1997, Paper No. 47).

of the nucleic acid sequence of interest and a second segment that is complementary to an oligonucleotide bound to a solid phase; (b) contacting the product of step (a) with the oligonucleotide bound to the solid phase; (c) thereafter separating materials not bound to the solid phase; (d) contacting the product of step (c) with the nucleic acid multimer, wherein the multimer comprises at least one oligonucleotide that is complementary to the second segment of the amplifier probe and a multiplicity of second oligonucleotide units that are complementary to a labeled oligonucleotide; (e) removing unbound multimer; (f) contacting the product of step (e) with the labeled oligonucleotide; (g) removing unbound labeled oligonucleotide; and (h) detecting the presence of label in the product of step (g) to detect the presence of the nucleic acid sequence of interest in the sample (see e.g., claim 12; pp. 3, 7, 24-27 and 31-32; Example 3, pp. 46-49). While Urdea exemplifies assays, reagents and kits for detecting hepatitis B virus, Neisseria gonorrhoeae and Chlamydia trachomatis, "Urdea does not teach the use of any HTLV-1 sequences nor a methodology for selecting any specific HTLV-1 sequences" (answer, p. 4, last sentence). In other words, Urdea does not disclose or suggest amplifier and capture probes having first segments selected from the group consisting of SEQ ID NOs. 6-41 and SEQ ID NOs. 42-53, respectively.

Seiki "reports the complete 9,032-nucleotide sequence of the proviral genome [of HTLV-1] cloned in 8ATK-1" (p. 3618, sentence bridging cc. 1-2; Fig. 2) and points "out that

the predicted viral genome ... could be tentative, because the provirus analyzed ... is that integrated in leukemia cells" (p. 3622, c. 2, first full para.).

Hogan discloses a method for preparing probes for use in hybridization assays which

comprises constructing an oligonucleotide that is sufficiently complementary to hybridize to a region of rRNA selected to be unique to a non-viral organism or group of non-viral organisms sought to be detected, said region of rRNA being selected by comparing one or more variable region rRNA sequences of said non-viral organism or group of non-viral organisms with one or more variable region rRNA sequences from one or more non-viral organisms sought to be distinguished" (abstract).

Ratner determined the sequences for nucleotides 1-5184, including the long terminal repeat (LTR), *gag*, protease gene, and *pol* sequences, of HTLV-1 isolates of Caribbean and African origin (abstract; p. 924, c. 1, para 3; Fig. 1) and stated that

[t]he limited sequence variation among HTLV-1 isolates suggests that diagnostic assays should be useful in detecting virtually all substrains of the virus. The positions of sequence variation outlined here should assist in the design of future diagnostic reagents. [P. 939, c. 2, para. 2.]

Stratagene describes two advantages of kits, convenience and quality control.

According to the examiner, it would have been obvious (a) to identify conserved regions of the HTLV-1 sequence disclosed by Seiki or Ratner (b) using the "the methodology of selection of particular primers as taught by Ratner or Hogan" (c) "to solve the problem of specific detection of a variety of HTLV-1 species" using the hybridization assay of Urdea (d) "since Ratner states 'The limited sequence variation among HTLV-1

isolates suggests that diagnostic assays should be useful in detection [sic, detecting] virtually all substrains of the virus. The positions of sequence variation outlined here should assist in the design of future diagnostic reagents.' " (answer, p. 6). Thus, the dispositive issue is whether the "methodology of selection" of Ratner or Hogan (or any other applied prior art reference) discloses or suggests the claimed synthetic oligonucleotides comprising a first segment selected from SEQ ID NOs. 6-41 and from SEQ ID NOs. 42-53 suitable for use as amplifier and capture probes, respectively, in a solution sandwich hybridization assay for HTLV-1.

First, we note that neither appellants nor the examiner appear to appreciate that Hogan is directed to nucleic acid probes for non-viral organisms based on unique rRNA sequences (see e.g., p. 3, ll. 22-30) found in 5S rRNA, 16S rRNA and 23S rRNA (see e.g., p. 9; claim 5). Hogan expressly states, "With the exception of viruses, all prokaryotic organisms contain rRNA molecules including 5S rRNA, 16S rRNA, and a larger rRNA molecule known as 23S rRNA" (emphasis added, p. 9, ll. 5-8). There is no evidence of record establishing that HTLV-1 contains 5S rRNA, 16S rRNA and/or 23S rRNA. The examiner has not provided any fact-based or reasoned explanation of why one of ordinary skill in the art would have looked to Hogan's method of selecting non-viral probes for detecting non-viral organisms for guidance in selecting viral nucleic acid probes for

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detecting a virus with any reasonable expectation of success of obtaining oligonucleotides comprising SEQ ID NOs. 6-53 as specifically claimed.

Second, the examiner has failed to point out, and we do not find, where Ratner provides any particular recognition or suggestion of the specific sequences, i.e., SEQ ID NOs. 6-53, required by the claimed invention.

None of Urdea, Seiki or Stratagene provide any particular recognition or suggestion of SEQ ID NOs 6-53 as required by the claimed invention. Therefore, in our view the examiner's rejection can be aptly characterized as an "obvious to try" rejection, i.e., obvious to try any nucleotide sequence contained within the 9,000-plus nucleic acid HTLV-1 genome. Simply opining that "any oligonucleotide probe from the HTLV-1 sequences of Ratner or Seiki are deemed functionally equivalent to the claimed oligonucleotides" (answer, p. 12), without a factual basis supporting that opinion, is insufficient to establish a conclusion of obviousness. As stated in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)

... what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (citations omitted).

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Accordingly, we find the examiner has not carried his burden of establishing a prima facie case of obviousness. Having concluded that the examiner has not established a prima facie case of obviousness, we do not reach the rebuttal declaratory evidence discussed in appellants' brief (pp. 9, 16, 19-22 and 30-32) and reply brief (pp. 8 and 11).

The rejections of claims 17-36 under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner alone or further in view of Stratagene are reversed.

OTHER MATTERS

The transitional phrases "comprising," "consisting essentially of" and "consisting of" are terms of art which define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. "Comprising" is open-ended and does not exclude additional, unrecited components or method steps, while "consisting of" is close-ended and excludes any component or step not specified in the claim. "Consisting essentially of" occupies a middle ground and limits the scope of a claim to the specified components or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. See e.g., the MPEP, 7th ed. (rev. 1, February 2000), at § 2111.03.

Here, the claims appear to use these terms in a non-traditional manner which gives rise to internal inconsistencies. For example, claim 17 recites an oligonucleotide which consists of a first segment which comprises, i.e., is open to the inclusion of, nucleotides over and beyond those of a specified a selected sequence, a second segment which consists of a sequence at least 90% homologous to another sequence, and optionally one or more noncomplementary sequences. Thus, the closed scope of the oligonucleotide of claim 17 is open to the inclusion of additional, unrecited nucleic acids and optional sequences.

As represented to us by appellants, this non-traditional term usage appears to have arisen at the suggestion of the examiner.⁴ However, in view of the apparent inconsistencies arising from this non-traditional term usage, appellants and the examiner should review any allowable claims prior to issuance in light of the art-recognized definition

⁴ According to appellants,

The first and second segments [of the claimed probes and probe sets] as defined constitute the only essential structural features of the optimized HTLV-1 probes. However, since a user can included additional "filler" sequence that is not complementary to HTLV-1 (and is therefore unlikely to impact hybridization) as described in the specification, the claims were originally written with the open claim language "comprising". In consultation with the Examiner of the predecessor application, it was considered preferable to employ the closed claim language "consisting of" and to specifically recite the noncomplementary sequence as an optional element. Applicants previously adopted the former Examiner's suggestions in an effort to expedite prosecution, and that language is reflected in the pending claims. [Emphasis added, brief, fn. 1.]

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CAROL A. SPIEGEL
Administrative Patent Judge

TONI R. SCHEINER
Administrative Patent Judge

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DECISION: **REVERSED**

Prepared By:

DRAFT TYPED: 02 Jul 01

FINAL TYPED: