

The opinion in support of the decision being entered today
is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KATSUYUKI SAITO, JAR-HOW LEE, and LINDLEY BLAIR

Appeal 2007-2363
Application 10/253,967
Technology Center 1600

Decided: September 11, 2007

Before TONI R. SCHEINER, DONALD E. ADAMS, and LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-6 and 8-20. We have jurisdiction under 35 U.S.C. § 6(b). Claims 1 and 9 are representative of the claims on appeal, and read as follows:

1. A method for detecting the presence of a target nucleic acid sequence on a sample nucleic acid strand comprising the steps of:

contacting a sample suspected of containing said target nucleic acid sequence with a diagnostic probe under hybridizing conditions;

wherein the nucleotide sequence of said diagnostic probe comprises (1) a first probe region at its 5'-end that is substantially complementary to a first target region characteristic of said target nucleic acid sequence, and (2) a second probe region, located 3' to said first probe region, where the second probe region is substantially complementary to a second target region characteristic of said target nucleic acid sequence on the target nucleic acid strand wherein the first and second probe regions on the diagnostic probe may be separated by a spacer region of nucleic acid, and further there exists an intervening sequence between the first and second target regions on the target nucleic acid strand;

wherein when said first and second probe regions are separated by a spacer region then said spacer region forms a non-self-hybridized loop under said selected conditions;

whereby for said selected hybridization conditions the first and second probe regions are such that the diagnostic probe is only stably hybridized to the target nucleic acid strand to form a detectable probe:target hybrid when the first probe region is substantially complementary to the first target region and the second probe region is substantially complementary to the second target region,

but wherein for said selected hybridization conditions the diagnostic probe is not stably hybridized to the target nucleic acid strand to form a probe:target hybrid detectable above a threshold indicative of stable hybridization when either the first probe region is not substantially complementary to the first target region or the second probe region is not substantially complementary to the second target region; and

detecting the presence or absence of the stable probe:target hybrid in the absence of elongation of the probe:target hybrid as an indication of the presence of the target nucleic acid sequence in the sample.

9. A method for detecting the presence of two or more target nucleic acid sequences on two or more sample nucleic acid strands comprising the steps of:

contacting a sample suspected of containing said target nucleic acid sequences with a diagnostic probe under hybridizing conditions;

wherein the first target nucleic acid sequence has a first target region and a first complementary target zone;

wherein the second nucleic acid sequence has a second target region and a second complementary target zone;

wherein the nucleotide sequence of said diagnostic probe comprises (1) a first probe region that is substantially complementary to a first target region characteristic of said first target nucleic acid sequence, and (2) a second probe region, where the second probe region is substantially complementary to a second target region characteristic of said second target nucleic acid sequence;

wherein said first and second probe regions on the diagnostic probe may be separated by a spacer region of nucleic acid wherein when said first and second probe regions are separated by a spacer region then said spacer region forms a non-self-hybridized loop under said selected conditions;

whereby for said selected hybridization conditions the first and second probe regions are such that the diagnostic probe is only stably hybridized to the target nucleic acid strand to form a detectable probe:target hybrid when the first complementary target zone is substantially complementary to the second complementary target zone, the first probe region is substantially complementary to the first target region, and the second probe region is substantially complementary to the second target region,

but wherein for said selected hybridization conditions the diagnostic probe is not stably hybridized to the target nucleic acid strand to form a probe:target hybrid detectable above a threshold indicative of stable hybridization when either the first complementary target zone is not substantially complementary to the second complementary target zone, or the first probe region is not substantially complementary to the first target region or the second probe region is not substantially complementary to the second target region; and

detecting the presence or absence of the stable probe:target hybrid in the absence of elongation of the probe:target hybrid as an indication of the presence of the target nucleic acid sequences in the sample.

The Examiner relies on the following reference.

Guo

5,780,233

Jul. 14, 1998

We affirm-in-part.

DISCUSSION

Claims 1-6 and 8-20 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Guo.

Appellants Group the claims into two Groups: Group I comprising claim 1 and the claims dependent thereon, i.e., claims 2-6, and 8, of which we choose claim 1 to be representative (Br.¹ 8),² and Group II comprising claim 9 and the claims dependent thereon, i.e., claims 10-20 (Br. 14), of which claim 9 is representative.

Guo is relied upon for teaching:

Contacting a sample suspected of containing said target nucleic acid sequence with a diagnostic probe under hybridizing conditions (see col. 3, line 63-67) wherein said probe comprises a first probe region at its 5'-end that is substantially complementary to a first target region and a second probe region located 3' to said first probe and is substantially complementary to a second target region, wherein the first and second probe regions may be separated by a spacer region and an intervening sequence (artificial mismatch sequence), wherein the spacer forms a non self hybridized loop (see fig. 1, the probe having a first and a second probe regions complementary to a first and a second target regions of a target separated by a one base mismatch (spacer) and two-base mismatches forming a non self-hybridized loop, [(]see col. 2, line 64-67, col. 4, line 47-67, col. 5, line 1, col. 7, line 16-44) under said conditions whereby the first and second probe regions only stably hybridize to form a stable probe:target complex, but wherein under said conditions the probe is not stably hybridized to the target strand to form a probe:target hybrid detectable above a threshold indicative of stable

¹ All references to the Brief (Br.) are to the Appeal Brief dated October 10, 2006.

² Claim 20, which depends from claim 1, and from claim 9, is also included here to the extent that it depends from claim 1.

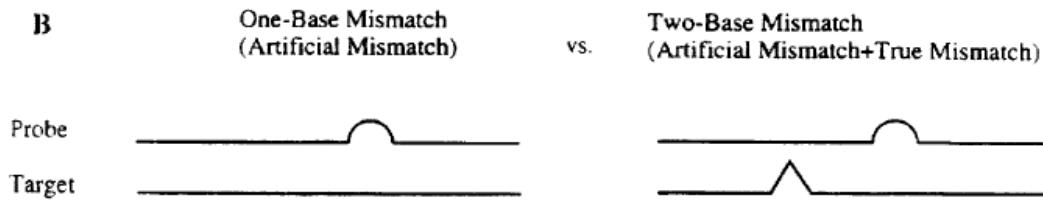
hybridization and detecting the presence or absence of the probe:target hybrid as an indication of the target nucleic acid sequence in the sample (see col. 5, line 1-67, col. 6, line 1-29, col. 7, line 2- 15, col. 8, line 59-67, col. 9, line 1-28).

(Answer 3.)

The burden is on the Examiner to set forth a *prima facie* case of unpatentability. *In re Glaug*, 283 F.3d 1335, 1338, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002). To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383, 58 USPQ2d 1286, 1291 (Fed. Cir. 2001).

Guo is drawn to a hybridization method for improving the ability to distinguish a first, control, nucleic acid, from a second, variant, nucleic acid (col. 2, ll. 14-18). The method employs a probe that generally, but not fully, complements the control nucleic acid (col. 2, ll. 19-26).

Panel B of Figure 1 is shown below, wherein the pointed mismatch represents a true mismatch and the rounded symbol represents an artificial mismatch (col. 4, ll. 41-46).



Panel B of Figure 1 of Guo represents the artificial mismatch hybridization strategy, in which the probe includes a purposely introduced single artificial mismatch so that the difference in duplex thermal stability is determined between a one base mismatch and a two base mismatch (col. 4, ll. 5863).

Guo teaches further that the variant target “can include a substitution, an insertion, a deletion, and a rearrangement of oligonucleotide nucleic acid relative to the target.” (Col. 4, ll. 41-46.) Moreover, according to Guo, the insertion or deletion can be as little as one nucleotide, with no upper limit (col. 4, ll. 8-11).

Thus, Guo reads on claim 1 when the variant, i.e., the true mismatch (pointed symbol) is an insertion of additional nucleotides in the target sequence. The portions of the target flanking the insertion read on “a first target region characteristic of said target nucleic acid sequence,” and “a second target region characteristic of the target nucleic acid sequence.” The insertion then reads on the “intervening sequence between the first and second target regions on the target nucleic acid strand.” Moreover, claim 1 recites “wherein the first and second probe regions on the diagnostic probe may be separated by a spacer region of nucleic acid,” and thus does not require that the probe have a spacer.

We therefore find that Guo teaches all of the limitations of claim 1, and the rejection is affirmed as to that claim, as well as to claims 2-8, and to claim 20 to the extent it depends on claim 1, as those claims stand or fall with claim 1.

As to claim 1, Appellants argue that the claims “recite polynucleic acid hybridization probes comprising *two probing regions* directed against a target nucleic acid having two target regions. In contrast, *Guo* is directed to a hybridization probe having a *single probing region* directed against a target nucleic acid having *a single target region*.” (Br. 8 (emphasis in original).)

Claim 1 is drawn to a method of detecting the presence of a target nucleic acid, wherein the target nucleic acid has two target regions. As discussed above, when the naturally occurring mismatch of Guo is an insertion, the portions of the target flanking the insertion read on “a first target region characteristic of said target nucleic acid sequence,” and “a second target region characteristic of the target nucleic acid sequence.”

Appellants argue further that Guo fails to anticipate the claim as “the single, double, or triple mismatched duplexes disclosed by Guo do not constitute ‘a spacer and an intervening sequence’ according to the claims.” (Br. 8). As discussed above, however, claim 1 does not require that the spacer be present in the probe, and when the naturally occurring mismatch is an insertion, it reads on the intervening sequence. Note that a reference need not have described an actual reduction to practice of an invention in order to serve as an anticipatory reference. *In re Siveramakrishnan*, 673 F.2d 1383, 1384, 213 USPQ 441, 442 (CCPA 1982); *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985).

Appellants argue further that the claims do not require perfect complementarity, and thus do not encompass a construction proposed by the rejection wherein the “spacer region” and the “intervening sequence” are the same length of 1, 2, or 3 bases (Br. 11). Such a construction, Appellants assert, Guo would “violate the claim requirement that the two probe regions and the two target regions *not be simultaneously contiguous.*” (*Id.* at 13 (emphasis in original)).

In the interpretation discussed above, however, there is no spacer region and the intervening region is at least one nucleotide, therefore, Appellants’ arguments are not persuasive. Moreover, while the claims do

not require perfect complementarity, they do not exclude it. And in any case, the introduction of the artificial mismatch as shown by the rounded symbol in Figure 1B would read a probe region that is “substantially complementary” to a region characteristic of the target nucleic acid sequence.

As to claim 9, Appellants argue that Guo “fails to disclose the element of first and second complementary target zones on first and second target nucleic acid sequences wherein the first complementary target zone is substantially complementary to the second complementary target zone.”

(Br. 15.)

The Examiner asserts in response that “Guo [] teach[es] target DNA as a PCR amplified DNA, which comprises duplex DNA with two strands thus the teachings of Guo [] do[] not exclude the limitations as claimed in claim 9 reciting detecting the presence or absence of two target sequences on two sample nucleic acid strands.” (Answer 10.)

Claim 9 requires a probe containing two probe regions, wherein the first probe region is “substantially complementary to a first target region characteristic of said first target nucleic acid sequence,” and the second probe region is “substantially complementary to a second target region characteristic of said second target nucleic acid sequence,” wherein the first target region and the second target region are on different nucleic acids. In addition, the first target nucleic acid sequence “has a first complementary target region and a first complementary target zone, and the second target nucleic acid sequence “has a second complementary target region and a second complementary target zone,” wherein “the first complementary target zone is substantially complementary to the second complementary target

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zone.” The Examiner does not point to, and we cannot find, assays in which the probe and the target nucleic acids have the recited properties, and we are thus compelled to reverse the rejection as to claim 9 and the claims dependent thereon, i.e., claims 10-19.

CONCLUSION

In summary, the rejection of claims 1-6 and 8-20 under 35 U.S.C. § 102(b) as being anticipated by Guo, is affirmed as to claims 1-8 and 20 (to the extent claim 20 depends from claim 1), and reversed as to claims 9-19.

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

AFFIRMED-IN-PART

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