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Paper No. 13

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte XIAN CHEN

Appeal No. 2001-1880
Application No. 09/273,835

ON BRIEF

Before WINTERS, SCHEINER and MILLS, Administrative Patent Judges.

MILLS, 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 1-26, which are all of the claims pending in this application.

Claim 1, 4, 5, 8, 14 and 21 are illustrative of the claims on appeal and read as follows:

1. A method for determining the nucleotide composition of an oligonucleotide which comprises the steps of:
 - (a) incorporating a stable, isotope-labeled form of one of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation in place of the ordinary nucleotide therein, the other three types of nucleotides in the oligonucleotide being unlabeled;
 - (b) measuring the mass peak of the unlabeled oligonucleotide using mass spectrometry;

- (c) measuring the mass peak of the labeled oligonucleotide using mass spectrometry;
- (d) obtaining the magnitude of the mass shift between the labeled oligonucleotide and the unlabeled oligonucleotide, whereby the number of isotope-labeled nucleotides in the oligonucleotide under investigation is determined; and
- (e) comparing the number of isotope-labeled nucleotides with the number of that type of nucleotide in a reference oligonucleotide.

4. The method for determining the nucleotide composition of an oligonucleotide as described in claim 3, wherein the chosen primers contain a sequence for the type IIS restriction enzyme.

5. The method for determining the nucleotide composition of an oligonucleotide as described in claim 1, wherein said step of incorporating a stable, isotope-labeled form of one of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation in place of the ordinary nucleotide therein is achieved using isothermal rolling-circle amplification.

8. A method for determining the nucleotide composition of an oligonucleotide which comprises the steps of:

- (a) incorporating a stable, isotope-labeled form of two of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation in place of the ordinary nucleotide therein, the other three types of nucleotides in the oligonucleotide being unlabeled;
- (b) measuring the mass peak of the unlabeled oligonucleotide using mass spectrometry;
- (c) measuring the mass peak of the labeled oligonucleotide using mass spectrometry;
- (d) obtaining the magnitude of the mass shift between the labeled oligonucleotide and the unlabeled oligonucleotide, whereby the number of isotope-labeled nucleotides in the oligonucleotide under investigation is determined; and
- (e) comparing the number of isotope-labeled nucleotides with the number of that type of nucleotide in a reference oligonucleotide.

14. A method for detecting polymorphisms in oligonucleotides which comprises the steps of:

- (a) incorporating a stable, isotope-labeled form of one of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation in place of the ordinary nucleotide therein, the other three types of nucleotides in the oligonucleotide being unlabeled;
- (b) measuring the mass peak of the unlabeled oligonucleotide using mass spectrometry;

(c) measuring the mass peak of the labeled oligonucleotide using mass spectrometry;

(d) obtaining the magnitude of the mass shift between the labeled oligonucleotide and the unlabeled oligonucleotide, whereby the number of isotope-labeled nucleotides in the oligonucleotide under investigation is determined.

21. A method for detecting polymorphisms in oligonucleotides which comprises the steps of:

(a) incorporating a stable, isotope-labeled form of two of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation in place of the ordinary nucleotide therein, the other three types of nucleotides in the oligonucleotide being unlabeled;

(b) measuring the mass peak of the unlabeled oligonucleotide using mass spectrometry;

(c) measuring the mass peak of the labeled oligonucleotide using mass spectrometry;

(d) obtaining the magnitude of the mass shift between the labeled oligonucleotide and the unlabeled oligonucleotide, whereby the number of isotope-labeled nucleotides in the oligonucleotide under investigation is determined.

The prior art references relied upon by the examiner are:

Arlinghaus et al (Arlinghaus)	5,780,232	July 14, 1998
Rothberg et al. (Rothberg)	5,972,693	Oct. 26, 1999
Lizardi (Lizardi)	5,854,033	Dec. 29, 1998

Grounds of Rejection¹

Claims 1-3, 6-10 and 13 stand rejected under 35 U.S.C. 102 as anticipated by

¹ Although claims 7 and 20 do not appear in the statement of the statutory basis of any rejection, they are discussed in the body of the statement of rejection, for example, Answer, pages 5 and 8. In addition, the appellant has understood these claims to be included in the rejections. Brief, pages 3 and 5. We note a prior objection to claims 7 and 20 was withdrawn by the examiner (Paper No. 8, page 2), however, as claims 7 and 20 appear to remain rejected in the answer, we treat the rejection of these claims as still pending. The examiner is reminded that all rejected claims should appear in the listing of the statutory basis of the rejection.

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Arlinghaus.

Claims 1-4, 6-11 and 13 stand rejected under 35 U.S.C. 103 as obvious over Arlinghaus in view of Rothberg.

Claims 1-26 stand rejected under 35 U.S.C. 103 as obvious over Arlinghaus and Rothberg in view of Lizardi.

DISCUSSION

In reaching our decision in this appeal, we have given consideration to the appellant's specification and claims, to the applied references, and to the respective positions articulated by the appellant and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the noted rejections, we make reference to the examiner's Answer for the examiner's reasoning in support of the rejection, and to the appellant's Brief and Reply Brief for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

Background

According to the specification (page 6, lines 14-18) the invention includes "the generation of nucleotide specific, stable isotope $^{13}\text{C}/^{15}\text{N}/^2\text{H}$ -labeled DNA coupled with analysis of the resulting mass shifts using mass spectroscopy (MS) to determine the number of each type of the labeled nucleotide." The claimed invention (claim 1) is

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directed to a method for determining the nucleotide composition of an oligonucleotide which comprises the steps of:

(a) incorporating a stable, isotope labeled form of one of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation in place of the ordinary nucleotide therein, the other three types of nucleotides in the oligonucleotide being unlabeled;

(b) measuring the mass peak of the unlabeled oligonucleotide using mass spectrometry;

(c) measuring the mass peak of the labeled oligonucleotide using mass spectrometry;

(d) obtaining the magnitude of the mass shift between the labeled oligonucleotide and the unlabeled oligonucleotide, whereby the number of isotope-labeled nucleotides in the oligonucleotide under investigation is determined; and

(e) comparing the number of isotope labeled nucleotides with the number of that type of nucleotide in a reference oligonucleotide.

“By incorporating stable, isotope-labeled nucleotides into oligonucleotides, 'mass tags' are introduced into PCR products, that is, the substitution of any or all of ^{13}C for ^{12}C , ^{15}N for ^{14}N , and ^2H for ^1H leads to a mass change of the oligomer.” Specification, page 6. With the presence of only one type (A, T, C or G) of labeled nucleotide in an oligomer, the overall mass change of the oligomer corresponds to the number of the labeled nucleotides in the oligomer, the other three types of nucleotides remaining unlabeled with their masses unchanged. Specification, pages 6-7. The specification indicates that “stable isotope labeling requires cells to be grown on a minimal medium containing 99% $(^{15}\text{NH}_4)_2\text{SO}_4$ or $^{15}\text{NH}_4\text{Cl}$ as the sole source of nitrogen for ^{15}N labeling, and/or 99% $^{13}\text{CH}_3\text{OH}$ or sodium $[1,2\text{-}^{13}\text{C}_2\ 99\%]$ acetate as the sole carbon source for ^{13}C labeling, and/or 99% $^2\text{H}_2\text{O}$ as the sole source of deuterium for ^2H labeling of DNA.” Specification, page 8.

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Claim Interpretation

Our appellate reviewing court stated in Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), cert denied, 481 U.S. 1052 (1987):

Analysis begins with a key legal question -- what is the invention claimed? Courts are required to view the claimed invention as a whole. 35 U.S.C. 103. Claim interpretation, in light of the specification, claim language, other claims and prosecution history, is a matter of law and will normally control the remainder of the decisional process. [Footnote omitted.]

“Although words in a claim are generally given their ordinary and customary meaning, a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is clearly stated in the patent specification or file history.” Vitronics Corp. v. Conceptor, Inc., 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576 (Fed. Cir. 1996). To that end, we also note that during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Appellant urges that step (a) as claimed, “incorporating a stable, isotope labeled form of one of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation in place of the ordinary nucleotide therein, the other three types of nucleotides in the oligonucleotide being unlabeled”, when read in view of the specification, “requires the isotopic labeling of all of one type of atom in a chosen nucleotide unit, for example, all of the carbon atoms. No atoms are introduced that do

not normally occur, and not atoms are attached to a nucleotide.” Brief, pages 7-8.

We are mindful that it is “improper to add extraneous limitations to a claim, that is limitations added wholly apart from any need to interpret what the patentee meant by particular words or phrases in a claim.” Amgen v. Hoechst Marion Roussel, Inc., 314 F3d 1313, 1393, 65 USPQ2d 1385 (Fed. Cir. 2003). Courts must take extreme care when ascertaining the proper scope of the claims, lest they simultaneously import into the claims limitations that were unintended by the patentee. See, e.g., Hogan AB v. Dresser Indus., Inc., 9 F.3d 948, 950, 28 USPQ2d 1936, 1938 (Fed. Cir. 1993).

However, it is also well settled that the claims are best understood in light of the specification of which they are a part. In the present case, appellant urges that, when the claims are read in view of the specification, the term “stable isotope-labeled form” takes on a specific meaning. In our view, when the claims are read in view of the specification as elucidated by the prosecution history, they require that all of one type of atom in a chosen nucleotide unit, for example, all of the carbon atoms, be labeled with an isotope, consistent with appellant’s interpretation. Appellant argues (Brief, page 8) that a “measurement according to the present invention involving less than all of a chosen element having been replaced by its isotopic form would not yield results that could be readily analyzed to yield the number of particular nucleotides present in an oligonucleotide.” Because the claimed invention would not yield results that could be readily analyzed if appellant's claim interpretation is not accepted, we find it reasonable to interpret that the claimed invention as supported by the specification, requires all of

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the carbon, nitrogen, or hydrogen atoms, be labeled with an isotope. We also find that appellant's stable isotope labeled nucleotides, as claimed, are limited to those nucleotides labeled with ^{13}C , ^{15}N and/or ^2H . Specification, page 6.

With this claim interpretation in mind, we review the prior art rejections made of the application.

35 U.S.C. § 102

Claims 1-4, 6-10 and 13 stand rejected under 35 U.S.C. 102 as anticipated by Arlinghaus.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”

Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). “It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is ‘anticipated’ if one of them is in the prior art.” Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985).

The examiner, in the Answer at pages 3-5, has indicated where each of the claimed steps is disclosed in the Arlinghaus reference. Arlinghaus (abstract) teaches a “DNA sequencing, mapping, and diagnostic process which includes the steps of labeling nucleotide segments or peptide nucleic acids (PNAs) with one or more atoms of specific stable or long-lived radioactive isotopes of a selected element that do not

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normally occur in DNAs, [oligodeoxynucleotides] ODNs or PNA's such that the nucleotide segment or PNS has specific, stable, or long lived radioactive isotope of a specified selected element at a terminal or interior position; hybridizing the labeled nucleotide segment or PNA to complementary nucleic acid segments or PNAs which are fixed on a hybridization surface; and, using mass spectrometric techniques, including RIS, to analyze the presence and position of the labeled hybridized nucleotide segments or PNAs which are bound to the fixed nucleotide segments or PNAs.”

Arlinghaus particularly mentions tin and rare earth isotopes, and isotopes attached to DNA fragments or ODNs.. Columns 2, 5 and 6. Claim 1 of Arlinghaus indicates that the isotopes are of an element that does not normally occur in DNAs or ODNs. Column 7, lines 57-59.

In response, appellant argues that the examiner fails to establish a prima facie case of anticipation because the claimed invention requires “isotopic labeling of all of one type of atom in a chosen nucleotide unit, for example, all of the carbon atoms.” Brief, page 8. In addition, appellant argues the claimed invention differs from the disclosure of Arlinghaus in that, “[n]o atoms are introduced that do not normally occur, and no atoms are attached to a nucleotide.” Id. Appellant argues that this interpretation of the claim language is supported by the meaning of “isotope labeled form” in the specification at page 8, lines 2-12; page 9, lines 5-15 and Table 1 of the specification. Id.

Appellant urges that Arlinghaus teaches that its “process includes the step of incorporating one or more atoms of a specific stable or long-lived radioactive isotope of a selected element on the ODN primer or the DNA, or in one or more of the deoxynucleotide triphosphates such that a DNA fragment has a specific stable or long-lived radioactive isotope of a specified selected element at a terminal or interior position.” Brief, page 8. Appellants also argues that Arlinghaus does not teach radioactive isotopes of a selected element that normally occur in DNAs, ODNs or PNAs, such as C-13, N-15 and H-2. Id.

The examiner responds arguing that “Arlinghaus teaches incorporating a stable, isotope-labeled form of one of the four nucleotide units of an oligonucleotide into the oligonucleotide under investigation, in place of the ordinary nucleotide therein, the other three types of nucleotides in the oligonucleotide being unlabeled (column 6, lines 18-51);[.]” Answer, page 9. The examiner suggests that, while appellant may argue that isotopic labeling of all of one type of atom in a chosen nucleotide unit, for example, all of the carbon atoms or nitrogen atoms or hydrogen atoms is not taught by Arlinghaus, the examiner does not find such a feature to be recited in the pending claims. Id.

We have determined that when the claims are fairly read in view of the prosecution history and specification, that appellant’s interpretation of the claims is supported, and reasonable.

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In view of our claim interpretation, we find the examiner has not adequately addressed appellant's arguments concerning differences of the claimed method from the disclosure of Arlinghaus. Thus, we cannot sustain the examiner's rejection of the claims in view of Arlinghaus.

35 U.S.C. 103

Claims 1-4, 6-11 and 13 stand rejected under 35 U.S.C. 103 as obvious over Arlinghaus in view of Rothberg.

The disclosure of Arlinghaus is provided in the Examiner's Answer, and discussed above. Rothberg is relied on by the examiner only for the disclosure of the use of chosen primers containing a sequence for type IIS restriction enzyme (Claim 4). Answer, page 5. We do not find that Rothberg overcomes the noted deficiencies of Arlinghaus. The rejection of the claims is reversed.

35 U.S.C. 103

Claims 1-26 stand rejected under 35 U.S.C. 103 as obvious over Arlinghaus and Rothberg in further view of Lizardi.

The disclosure of Arlinghaus and Rothberg is provided in the Examiner's Answer, and discussed above. Lizardi is relied on by the examiner for the disclosure of the use of isothermal rolling circle amplification. Answer, page 7. We do not find that Lizardi overcomes the noted deficiencies of Arlinghaus and Rothberg. The rejection of

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the claims is reversed.

CONCLUSION

In view of the above, the rejections of claims 1-3, 6-10 and 13 under 35 U.S.C. 102 as anticipated by Arlinghaus; claims 1-4, 6-11 and 13 under 35 U.S.C. 103 as obvious over Arlinghaus in view of Rothberg; and claims 1-26 under 35 U.S.C. 103 as obvious over Arlinghaus and Rothberg in view of Lizardi are reversed.

REVERSED

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SHERMAN D. WINTERS)	
Administrative Patent Judge)	
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