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465 Columbus Avenue
Suite 340
Valhalla, NY 10595

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LU, FRANK WEI MIN

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debbie.henn@philips.com
patti.demichele@Philips.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANKE PIERIK and HENDRIK ROELOF STAPERT

Appeal 2014-004656
Application 13/121,206
Technology Center 1600

Before DEMETRA J. MILLS, ERIC B. GRIMES, and
RICHARD J. SMITH, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for not being directed to patentable subject matter and for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF CASE

According to the Specification,

> The present invention relates to a method for immobilizing nucleic acids on a support, comprising the provision of a nucleic acid with a stretch of nucleotides of only one basetype and the immobilization of said nucleic acid on a support by crosslinking by light, wherein said crosslinking by light is performed at a wavelength of about 300-500 nm, preferably at a wavelength of 365 nm.

Spec. 1.

The nucleic acid to be immobilized on the support material may according to a further preferred embodiment be represented by the formula I:

$$5'\text{-}Y_n\text{-}X_m\text{-}B_r\text{-}X_p\text{-}Z_q\text{-}3'$$

In formula I Y and Z are stretches of nucleotides of only one basetype, wherein Y and Z can be of the same or of a different basetype; X is a spacer; B is a sequence of more than one basetype and n, m, r, p and q are numbers of nucleotides in the nucleic acid, for which the following conditions may apply: n, m, p, q, r > 1; n, m, r > 1 and p, q = 0; p, q, r > 1 and n, m = 0; n, q, r > 1 and m, p = 0; n, r > 1 and m, p, q = 0; q, r > 1 and n, m, p = 0. The term "stretch of nucleotides of only one basetype" … relates to nucleotides composed of only one kind of base, e.g. thymine, guanine, adenine, cytosine or uracil or any functional equivalent derivative thereof.

Spec. 13.

Element(s) X of Formula I of the present invention may additionally be present as spacer element(s), i.e. as regions comprising sequences of undefined nature. More preferably element X may be composed of abasic nucleotides. The term "abasic" relates to positions in the nucleic acid molecule, at which no[] basic residue is present. Abasic regions or stretches of a nucleic acid are, thus, only composed of sugar phosphate backbone elements. Such an abasic structure may have a positive influence on the flexibility of the entire molecule, in particular with respect to element B of the molecule. The inventors could show that *the presence of abasic sites have a positive influence on the capability of the immobilized molecule to specifically interact with or hybridize to a target probe* (see Example 4 and Fig. 5). A separation of the portions of the molecule used for immobilization, e.g. Y or Z of formula I, form the portion(s) of the molecule used for specific hybridization, e.g. B of formula I, by way of introducing *spacer elements comprising abasic sites may significantly decrease unspecific hybridization reactions in the portion of the molecule used for specific hybridization*, e.g. B of formula I.

Spec. 14, italicized emphasis added.

The following claims are representative.

1. A method for immobilizing nucleic acids on a support, comprising the steps of:

(a) providing a nucleic acid with a stretch of nucleotides of only one basetype; and

(b) immobilizing said nucleic acid on a solid support by crosslinking by light, wherein said crosslinking by light is performed at a wavelength of about 300-500 nm and wherein said crosslinking is performed using an amount of energy ranging from about 0.5 Joule/cm^2 to about 10 Joule/cm^2 and further wherein said nucleic acid includes at least one spacer comprising one or more abasic sites between nucleotides.

14. Use of nucleic acids, which are immobilized according to the method of claim 1, for the production of a nucleic acid array.

Cited References

Dyson et al.	US 4,889,606	Dec. 26, 1989 ("Dyson")
Mulligan et al.	US 2002/0077471 A1	June 20, 2002 ("Mulligan")

Cole, *Psoralen Monoadducts and Interstrand Cross-links in DNA*, 254 Biochim. Biophys. Acta 30–39 (1971) ("Cole").

Serge Boiteux and Jacques Laval, *Coding Properties of Poly(deoxycytidylic acid) Templates Containing Uracil or Apyrimidinic Sites: In Vitro Modulation of Mutagenesis by Deoxyribonucleic Acid Repair Enzymes*, 21 Biochem. 6746–6751 (1982) ("Boiteux").

Technical Note from Millipore, Colony Lifts Using Immobilon™ –NY+ Membrane 1–10 (1999) (hereinafter "Millipore").

Nakano et al., *Photoactive covalent attachment of deoxyribonucleic acid on gold with double-strand specificity using self-assembled monolayers containing psoralen*, 578 Analytica Chimica Acta 93–99 (2006) ("Nakano").

Grounds of Rejection[1]

1. Claim 14 is rejected under 35 U.S.C. § 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process.
2. Claims 1–4, 7, 9, 11, 14, and 18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Millipore in view of Mulligan.
3. Claims 1–4, 7, 9, 11, 14, and 18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Millipore in view of Dyson and Mulligan.
4. Claims 1–4, 7, 9, 11, 14, 16, and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Millipore in view of Nakano and Mulligan.
5. Claims 1–4, 6, 7, 9–11, 14, 16, and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakano in view of Cole and Mulligan.
6. Claims 5 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakano in view of Cole and Mulligan, as applied to claims 1–4, 6, 7, 9–11, 14, 16, and 18 above, and further in view of Boiteux.

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[1] The rejection of claim 2 under 35 U.S.C. § 112(b) has been withdrawn by the Examiner. Ans. 3.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Answer at pages 3–16.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g.*, *Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted).

Rejection 1- § 101

The Examiner rejects claim 14 under 35 U.S.C. § 101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. § 101." Final Act. 5.

Appellants argue, in response, that

> Claim 14 explicitly recites the use of nucleic acids "which are immobilized <u>according to the method of claim 1</u>." Since claim 14 depends from claim 1, claim 14 thus "include[s] all the limitations of" claim 1, in accordance with MPEP § 608.01(i). As such, claim 14 includes the steps of, for example, "providing a nucleic acid . . ." and "immobilizing said nucleic acid . . ." as recited in claim 1.

Br. 11. Appellants further argue that, "MPEP § 608.01(i) explains: 'Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim.'" *Id.*

We find that the Appellants have the better argument. Claim 14 is dependent upon claim 1 which provides method steps for "immobilizing said nucleic acid on a solid support by crosslinking by light." Thus, claim 14 is directed to a method of using claim 1's method of immobilizing nucleic acids for producing a nucleic acid array. We find that claim 14 recites sufficient process steps through its claim dependency, and the rejection under 35 U.S.C. § 101 is reversed.

Rejections 2–4

We address obviousness Rejections 2–4 together as they share a single dispositive issue: Whether the Examiner has provided a reasonable basis for concluding that the combination of cited prior art suggests a reason to combine Millipore and Mulligan to arrive at the claimed invention.

In each of Rejections 2–4, the Examiner relies on Millipore for disclosing

> a method for immobilizing nucleic acids on a support, comprising the steps of: (a) providing a nucleic acid with a stretch of nucleotides of only one basetype (ie., the positive clone of JM109 transformed with a plasmid pLH2 must have a stretch containing two GG); and (b) immobilizing said nucleic acid on a solid support by crosslinking by light, wherein said crosslinking by light is performed at a wavelength of about 300-500 nm (ie., 254 nm) and wherein said crosslinking is performed using an amount of energy ranging from about 0.5 Joule/cm^2 to about 10 Joule/cm^2 (ie., 5000 mJoules/ cm^2).

Final Act. 7, 9, 11. Mulligan is relied on for the disclosure of "a 205 bp DNA fragment having an abasic site from lacI gene (see pages 4-6, Examples 1-5)." Final Act. 8. The Examiner concluded that

> it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 1 and 7 wherein said nucleic acid includes at least one spacer comprising one or more abasic sites between nucleotides and X is a space including abasic nucleotides in view of the prior arts of Technical Note from Millipore and Mulligan *et al.*[] One having ordinary skill in the art would have been motivated to do so because Mulligan et al., have shown a 205 bp DNA fragment having an abasic site from lacI gene (see pages 4-6, Examples 1-5) and the simple substitution of one kind of nucleic acid (ie., the nucleic acid without one or more abasic sites taught by Technical Note from Millipore) from another kind of nucleic acid . . . would have been *prima facie* obvious.

Final Act. 8–9.

We do not find that the Examiner, on this record, has provided a sufficient reason, motivation, or rational basis to combine Millipore and Mulligan. *Compare*, *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). In the first instance, the Examiner has not pointed to a specific nucleotide sequence in plasmid pLH2 disclosed in Millipore, having a stretch containing two GG. No sequence of plasmid pLH2 is provided in the Millipore reference. Furthermore, the Examiner has provided no rational basis or reason to combine Millipore and Mulligan, or to select or substitute a nucleic acid which includes at least one spacer and one or more abasic sites between nucleotides, or substitute the oligonucleotide sequence AB-134 of Mulligan (Ans. 6), for the plasmid sequence of Millipore.

Millipore is directed to a positively charged nylon membrane which can be used for performing colony lifts. DNA is fixed to the membrane by UV crosslinking. Abstract; p. 1. Mulligan is directed to a method for improving the sequence fidelity of synthetic, double-stranded oligonucleotides to prevent undesired products of oligonucleotide synthesis; such as side products, truncated products or products from incorrect ligation. Mulligan, Abstract, ¶¶ 16 and 25. Mulligan discloses that synthetic molecules containing natural bases can be separated from those containing synthetic failures and that

> Oligonucleotide synthesis (e.g., chemical synthesis) can generate a variety of side products. For example, side products include an abasic residue (e.g., an apurinic or apyrimidinic residue), diaminopurine, an incompletely deprotected G, and uridine. For purposes of the present invention, the common feature of the side products is that these unnatural bases destabilize the double-stranded oligonucleotides in which they are incorporated, such that these synthetic failures melt at a lower temperature than synthetic double-stranded oligonucleotides containing only natural bases.

Mulligan ¶ 25. The Examiner provides no clear nexus or basis as to why one of ordinary skill in the art would select a nucleic acid sequence which includes at least one spacer comprising one or more abasic sites between nucleotides and substitute it for the plasmid disclosed in Millipore.

Appellants have discovered that introducing spacer elements comprising abasic sites may significantly decrease the problem of unspecific hybridization reactions in the portion of the molecule used for specific hybridization. Spec. 14. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of

invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR Int'l Co. v. Teleflex, Inc.,* 550 U.S. 398, 419–20 (2007). In the present case, however, none of the cited references acknowledges or addresses Appellants' problem. While the motivation to combine references does not have to be identical to Appellants' to establish obviousness, a reference should be reasonably pertinent to the problem with which the inventor is involved or should logically commend itself to an inventor's attention in considering his problem. *In re Clay*, 966 F.2d 659, 660 (Fed. Cir. 1992). The Examiner has not established either the reasonable pertinence of Mulligan to Millipore, or their relation to the problem solved by Appellants on the evidence before us.

Rejections 2–4 are reversed.

Rejections 5 and 6

We address obviousness Rejections 5 and 6 together as they share a single dispositive issue: Whether the Examiner has provided a reasonable basis for concluding that the combination of cited prior art suggests a reason to combine Nakano and Mulligan to arrive at the claimed invention.

The Examiner relies on Nakano for the disclosure of

> a method for immobilizing nucleic acids on a support, comprising the steps of: (a) providing a nucleic acid (eg., K-ras ODN) with a stretch of nucleotides of only one basetype (eg., GG); and (b) immobilizing said nucleic acid on a solid support by crosslinking by light, wherein said crosslinking by light is performed at a wavelength of about 300-500 nm (ie., 320-400 nm)

Final Act. 14. Mulligan is directed to a method for improving the sequence fidelity of synthetic double-stranded oligonucleotides to prevent undesired products of oligonucleotide synthesis; such as side products, truncated products or products from incorrect ligation. Mulligan, Abstract, ¶¶ 16 and 25. Again, the Examiner provides no clear nexus or basis as to why one of ordinary skill in the art would select a nucleic acid which includes at least one spacer comprising one or more abasic sites between nucleotides, or the nucleic acid sequence of Mulligan, and include it in the method of Nakano.

Rejections 5 and 6 are reversed.

CONCLUSION OF LAW

The cited references do not support the Examiner's obviousness rejections, which are reversed. The 35 U.S.C. § 101 rejection is also reversed.

REVERSED