

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte DIANE D. ILSLEY, PETER TSANG,
MICHAEL P. CAREN, and DOUGLAS A. AMORESE

Appeal No. 2006-1547
Application No. 10/114,668

ON BRIEF

Before SCHEINER, GRIMES, and LEOVITZ, Administrative Patent Judges.

LEOVITZ, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to methods of assaying nucleic acid analytes using DNA primer arrays. The examiner has rejected the claims as unpatentable over prior art. We have jurisdiction under 35 U.S.C. § 134. We affirm-in-part and enter new grounds of rejection.

Background

The claimed invention is in the field of nucleic acid detection, where DNA arrays are utilized to determine the presence of a nucleic acid in a sample. According to the "Summary of the Invention," DNA primer arrays are provided that facilitate the synthesis of target nucleic acids on the array surface at distinct locations where a DNA primer has

hybridized to a target nucleic acid analyte. Specification, ¶ 6. In addition to the DNA primer, a DNA polymerase, dNTPs, and other reactants required for DNA synthesis can be present at the distinct locations which comprise the array.

Discussion

1. Claim construction

Claims 1-39 are on appeal. The claims do not stand or fall together. Appellant presented arguments for three separate groups of claims. Appeal Brief, page 11. We consider the following claims representative of the claims subject to each rejection:

Group I

1. A method of assaying a sample for the presence of one or more nucleic acid analyte members of a nucleic acid analyte set, said method comprising:
(a) providing an array of at least two distinct DNA primer compositions immobilized on a surface of a solid support at distinct locations, wherein each of said at least two distinct DNA primer compositions comprises a DNA primer that hybridizes under stringent conditions to a different member of said nucleic acid analyte set and at least one template dependent primer extension reactant comprising a pulse-jet deposited polymerase;
(b) contacting each of said at least two distinct DNA primer compositions of said array with said sample under DNA synthesis conditions sufficient to produce labeled target nucleic acids at locations on said surface where a nucleic acid analyte present in said sample hybridizes to a DNA primer to produce a duplex nucleic acid;
(c) detecting the presence of labeled target nucleic acids on said array surface to obtain assay data; and
(d) employing said assay data to determine the presence of one or more nucleic acid analytes in said sample.

Group II

8. The method according to Claim 1, wherein said providing step comprises providing an array of DNA primer compositions in a dry, storage stable format, wherein each DNA primer composition includes: (a) a DNA primer; (b) pulse-jet deposited polymerase; and (c) at least one of an effective amount of a DNA synthesis reagent selected from the group consisting of: (i) dATP; (ii) dGTP; (iii) dTTP; (iv) dCTP; and (v) at least one type of labeled dNTP.

Group III

29. A method of assaying a sample for the presence of one or more nucleic acid analyte members of a nucleic acid analyte set, said method comprising:

(a) providing an array of at least two distinct DNA primers immobilized on a surface of a solid support at distinct locations, wherein each of said at least two distinct DNA primers hybridizes under stringent conditions to a different member of said nucleic acid analyte set;

(b) contacting by pulsejet deposition each of said at least two distinct DNA primers of said array with said sample and an effective amount of all of the following DNA synthesis reagents: (i) dATP, (ii) [sic] dGTP; (iii) dTTP; (iv) dCTP; (v) at least one type of labeled dNTP; (vi) a template dependent DNA polymerase; (vii) a divalent cation; (viii) a buffering salt; and (ix) an RNase inhibitor

under DNA synthesis conditions sufficient to produce labeled target nucleic acids at locations on said surface where a nucleic acid analyte present in said sample hybridizes to a DNA primer to produce a duplex nucleic acid;

(c) detecting the presence of labeled target nucleic acids on said array surface to obtain assay data; and

(d) employing said assay data to determine the presence of one or more nucleic acid analytes in said sample.

Independent claims 1 and 29 require “an array of at least two distinct DNA primer compositions immobilized on a surface of a solid support at distinct locations.” An “array” is defined in the specification to mean “a substrate having a plurality of binding agents stably attached to its surface, where the binding agents may be spatially located across the surface of the substrate in any number of different patterns.” Specification, page 3, ¶ 14. Various array formats are described, including arrays where the distinct locations are separated by physical barriers. Id., ¶ 30, 33.

In the claimed invention, the array-binding agents are DNA primers. A primer is a short sequence of nucleotides that is specific for a single mRNA molecule. Id., ¶ 31. The primers are located at “distinct locations” on the solid support. As indicated in the specification, the “distinct locations” are different regions on the surface of the array

which are spatially separated from each other. See, e.g., *Id.*, ¶¶ 27, 32, and 33. The latter is consistent with the many examples described in the application. See, e.g., *Id.*, page 27, Example II. B.

The primer compositions which are “immobilized” on the surface of the support contain distinct DNA primers, a pulse-jet deposited polymerase, and other reactants. With respect to the DNA primers, the term “immobilized” is described in the application as meaning “stably associated with,” and can be achieved through either covalent or non-covalent bonding. *Id.*, ¶¶ 28, 31, 92. There is no express definition of how the polymerase (and other reactants in dependent claims) are immobilized on the surface, but most of the examples involve deposition by pulse-jet technology, so we construe “immobilized” to include reactants which have been associated with the support by pulse-jet deposition. *Id.*, ¶¶ 46, 47. When pulse-jet fluid deposition is utilized to immobilize a reactant, fluid containing the reactant (primer, polymerase, dNTP, etc) is expelled on to the surface, where it can be optionally covalently bound. ¶¶ 32, 69. Thus, we construe “immobilized on a surface of a solid support” broadly to include the deposit of a fluid, and not to require covalent linkage.

“Pulse-jet” is a technology for delivering small sample volumes to a surface or location. The technology is admitted to be prior art for both DNA (*Id.*, ¶¶ 5, 47) and proteins (*Id.*, ¶ 5). “Thermal inkjet deposition” is a type of pulse-jet technology. *Id.*, ¶¶ 48, 62-72. The terms “inkjet” and pulse-jet” are used interchangeably herein.

The phrase “solid support” is not utilized in the specification, although it is recited in the original claims. Instead, the specification repeatedly refers to a “substrate surface.” *Id.*, e.g., ¶¶ 14, 28, 32. There is no restriction described for the substrate.

Id., e.g., ¶ 30. Glass is the only disclosed example. Id., ¶ 92, Examples I and II.

Claims 1 and 8 also refer to a “pulse-jet deposited polymerase” which is a component of the claimed DNA primer composition. The application describes the use of pulse-jet (e.g., inkjet) to deposit the array reagents, including polymerases. Id., ¶ 47-51. The phrase “pulse-jet deposited polymerase” is not expressly defined in the specification, but given that “pulse-jet” is extensively described as a means for depositing protein reagents, including enzymes having polymerase activity, we construe the phrase to mean that the polymerase was immobilized on the solid support by pulse-jet deposition. This technology facilitates the deposition of reactants at discrete locations on the array surface. Id., ¶ 26, 32, 56.

Claim 8 and 19 also refer to the primer compositions being “in a dry, storage stable format.” This is expressly defined in the specification: “By dry, storage stable format is meant an array that is present in dry form, where the various reagents compositions making up the array are dry, i.e., are not fluid compositions.” Id., ¶ 56. In one embodiment, dehydration is described to produce a dry sample on the substrate surface by removing the water. Id., ¶ 53.

2. Indefiniteness under §112, second paragraph

Claims 1-28 were rejected under 35 U.S.C. § 112, second paragraph as indefinite in the recitation of a “pulse-jet deposited polymerase.” The examiner stated that “it is unclear what makes a polymerase a pulse-jet deposited polymerase. The specification and the art do not specifically define what a pulse-jet deposited polymerase encompasses.” Examiner’s Answer, page 3.

A specification must conclude with claims “particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.” 35 U.S.C. §112, ¶ 2 (2000). The purpose of 35 U.S.C. §112, ¶ 2, is to “reasonably apprise those skilled in the art of the scope of the invention.” Miles Labs., Inc. v. Shandon, Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993). In examining the claims of an application, the PTO is permitted to “adopt the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification.” In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed.Cir.1997); In re Crish, 393 F.3d 1253, 1256, 73 USPQ2d 1364, 1367 (Fed.Cir. 2004).

Claim 1 requires a DNA primer composition that comprises a “pulse-jet deposited polymerase.” “Pulse-jet deposited” has been construed to define the method (“pulse-jet”) by which the polymerase is immobilized (“deposited”) on the surface of the solid support. It is a meaningful limitation since it would localize the polymerase to a discrete region on the solid support by virtue of the jet-pulse process. See, Specification, ¶ 26. The polymerase is not imbued with any additional distinguishing features, other than it possess “template dependent primer extension” polymerase activity as expressly recited in the claim. Our construction relies on both the ordinary usage of the phrase and the written description which describes the use of pulse jet deposition protocols to immobilize DNA polymerase. Id., page 27, B. The construction is consistent with the structure of independent claims 1 and 19 which require the “pulse-jet deposited polymerase” to be a component of the “DNA primer composition” which, itself, is

immobilized at a “distinct location” on the claimed primer array. Thus, we agree with Appellant that the claim term is definite under § 112, second paragraph, and accordingly, reverse the rejection of claims 1-28.

4. Anticipation under § 102

The examiner rejected claims 1, 3, 4, 12, 14, 16-18, and 39 as being anticipated under 35 U.S.C. § 102(a) and (e) by Ulfendahl¹; claims 1, 3, 4, 8, 14, and 16-18 as being anticipated under § 102(b) by Ulfendahl-WO²; and claims 1-4, 6, 7, 12, and 14-16 as being anticipated under § 102(a) and (e) by Yu³.

Ulfendahl

Although it was stated in the Answer that the U.S. Patent and WO publication by Ulfendahl have identical disclosures (Answer, page 6), the rejected claim groups were different for each reference and no explanation was given. Claims 12 and 39 were included in the rejection over the U.S. patent, but not the WO; Claim 8 was included in the rejection over the WO, but not the U.S. patent. Appellant did not comment on this discrepancy.

In setting forth the grounds of the rejection, the examiner only referred to Ulfendahl’s U.S. Patent. In view of this, and because the examiner did not explain the basis for the rejection of claim 8, we will consider the rejection only as it applies claims 1, 3, 4, 12, 14, 16-18, and 39 for the U.S. Patent.

¹ Ulfendahl, U.S. Patent 6,280,954, issued Aug. 28, 2001

² Ulfendahl (Ulfendahl-WO), WO99/39001 published Aug. 05, 1999

³ Yu et al. (Yu) U.S. Pub. Pat. App. No. 2001/0036632, published Nov. 1, 2001

Ulfendahl describes methods for identifying and characterizing organisms based on differences in their DNA. Generally, these methods are known as DNA fingerprinting, because each organism has a different DNA sequence that is analogous to how fingerprints differ between individuals. In the specific methods described in the Ulfendahl patent, DNA primers (“probes”) are immobilized to a substrate, hybridized to a matching a nucleic acid, and then subjected to enzyme extension using a DNA polymerase (where the DNA probe serves as a primer for extension of a DNA strand complementary to the DNA probe). See, Ulfendahl, Fig. 1. The primer extension product is detected. Id., column 8, lines 14-35. These features are pointed out in the Answer (e.g., pages 6-7), and undisputed, except for one aspect. Appellant argues that the claimed invention is distinguished over Ulfendahl because the latter does not “teach or disclose a DNA composition containing a pulse-jet deposited polymerase.” Appeal Brief, page 15, lines 7-8.

Anticipation under § 102 requires a showing that each limitation of a claim is found in a single reference, either expressly or inherently. Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1369, 77 USPQ2d 1321, 1325 (Fed. Cir. 2005). We agree with the examiner’s determination that Ulfendahl’s U.S. Pat. No. 6,280,954 discloses the limitations set forth in claims 1, 3, 4, 12, 16-18, and 39, meeting the requirements for anticipation.

Example 1 of Ulfendahl describes a primer extension method performed in a microtiter well plate. Id., column 7, lines 3-35. The latter is essentially a flat plate having a plurality of physically separated depressions that form small wells in which reactions can occur. The array recited in appealed claim 1 is not limited to any

particular format or structure, but has been construed to include an array where the distinct locations are physically separated, including, e.g., “raised structures or walls arising from the surfaces of the array.” Specification, page 8, ¶ 34. The primers “were bound to microtitre plate wells” and other reactants, including the polymerase, were added as fluid drops to the wells. Ulfendahl, column 7, lines 30-50. The term “immobilized” has been construed broadly to include these types of reactant localization. Therefore, the microtiter well array disclosed in Ulfendahl fulfills the requirement in claim 1 for an “array of ... distinct DNA primer compositions immobilized on a surface of a solid support at distinct locations.”

Each individual well described in Ulfendahl contains, for instance, buffer, dNTPs, fluorescent labeled dCTP, and DNA polymerase. Ulfendahl, column 7, line 35-column 8, line 35; column 10, lines 20-25. Thus, the DNA polymerase is at distinct regions on the solid support, i.e., in a well. This arrangement satisfies the claim requirement that the “pulse-jet deposited polymerase” is immobilized at distinct locations on the solid support.

This conclusion is not changed by our agreement with Appellant that the polymerase described in Ulfendahl is not “pulse-jet deposited.” The latter limitation has been construed to restrict the geographical location of the polymerase, but to affect no other characteristic of it. “Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product.” In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Giving the phrase “pulse-jet deposited polymerase” its broadest reasonable meaning, the examiner properly rejected the claimed method over Ulfendahl (as well as the other prior art discussed below), shifting the burden to appellant to distinguish it from, e.g., a polymerase immobilized by other processes. Appellant did not provide any arguments in rebuttal.

Finally, we note that the DNA primer composition of claim 1 is expressly described to be present at a “distinct location,” and the polymerase is a component of it.

Since Appellant distinguished no other features of the claim from the prior art, we affirm the anticipation rejection with respect to claim 1, 3, 4, 12, 14, 16-18, and 39.

Yu

As described in the Answer, Yu discloses a primer extension technology similar to Ulfendahl where PCR is performed in situ on a microarray. Answer, pages 4-5; Yu, ¶ 16. Once again, the only fact in dispute is whether Yu describes a “pulse-jet deposited polymerase.” Brief, page 14. The examiner applied the rejection because “polymerases are inherently capable of being deposited by pulse-jet or ink jet,” but made no finding that the polymerase was restricted to a distinct location on the array as required by other limitations in the claim. Answer, page 28.

Claim 1 requires that the “pulse-jet deposited polymerase” be immobilized at distinct locations on the array. We can find no evidence in Yu or in the Answer that the polymerase is so localized. To the contrary, it appears that it was distributed over the entire array surface. Yu, ¶ 106-107. Anticipation requires a showing that each element of the claim is identifiable in a single reference. Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1369, 77 USPQ2d 1321, 1325 (Fed. Cir. 2005). In the absence of this

feature, the rejection cannot be maintained. Accordingly, we reverse the § 102 rejection over Yu for claims 1-4, 6, 7, 12, and 14-16.

5. Obviousness based on the Kosak patent

Claims 1-8, 10-12, 14, 17-21, 25, 27-28, and 39 were rejected under 35 U.S.C. § 103 as unpatentable over Kosak⁴ in view of Nikiforov⁵. Claims 13, 22, and 23 were rejected under 35 U.S.C. § 103 as unpatentable over Kosak in view of Nikiforov, and further in view of Shipwash⁶.

Claims 1-12, 14-16, 19-21, and 24-26 were rejected under 35 U.S.C. § 103 as unpatentable over Kosak in view of Yu. Claims 13, 22-23, 29-38 were rejected under 35 U.S.C. § 103 as unpatentable over Kosak in view of Yu, and further in view of Shipwash. Claims 13, 22-23, 29-38 were rejected under 35 U.S.C. § 103 as unpatentable over Kosak in view of Yu, and further in view of Church⁷.

Group I, claims 1-7, 12-18, and 39

Since each of these rejections relies on Kosak as the primary reference, we will address them jointly as they relate to Group I claims.

The rejections are based on the disclosure by Kosak of a DNA oligonucleotide primer array comprising reagents for carrying out various nucleic acid technologies, including polymerase chain reaction, reverse transcriptase reactions, and nucleic acid sequencing. Kosak, Abstract. The basic method involves trapping reagents for performing nucleic acid polymerization reactions in a material. Upon heat treatment, the reagents are released from the material and available for reaction. Id., column 3, lines

⁴ Kosak et al. (Kosak), U.S. Patent 5,643,764, issued Jul. 01, 1997

⁵ Nikiforov et al. (Nikiforov), Nucl. Acid Res., 22:4167-4175, 1994

⁶ Shipwash, U.S. Pub. Pat. App. No. 2002/0058273, published May 16, 2002

5-15. Examples include liposomes (column 7, line 5) and wax beads, where an aqueous reagent is coated with a waxy polymer (e.g., column 12, lines 50-60).

According to Kosak, “The reagent entrapped within wax beads solves the problems of adding stepwise, one or more essential reagents into a reaction medium when needed, without reopening containers or interrupting the procedure.” Id., column 3, lines 1-5.

See also, Answer, pages 8-9. This reference in combination with Nikiforov or Yu was stated by the examiner to render obvious the claims. Yu was discussed above, and Nikiforov is described on page 10 of the Answer.

The Shipwash patent was further relied upon by the examiner in rejecting claims 13, 22, and 23 for its general teaching of pulse-jet technology. In ¶ 179, Shipwash states: “A range of new micropipetting systems based on ink-jet principles have been developed for delivery of nanoliter volumes of samples and reagents to microwells (for example, see, Rose and Lemmo (1997) Lab Automat News: 2:12-9; Fischer-Fruholz (1998) American Lab; Feb 46-51).” The examiner argued that it would have been obvious to have utilized this technology “to enable more rapid, automated and precise delivery of the reactants to the microwells.” Answer, page 16.

The examiner bears the initial burden of showing unpatentability. See, e.g., In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

A prima facie case of obviousness requires evidence that the prior art disclosed or suggested all of the elements of the claimed invention, and that those skilled in the art would have been motivated to combine those elements with a reasonable expectation

⁷ Church et al. (Church), U.S. Pub. Pat. App. No. 2002/0127552, published Sep. 12, 2002

of success. See In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970); In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991).

The primary objection raised by Appellant was that neither Kosak, nor any of the secondary references, disclosed or suggested a “pulse-jet deposited polymerase” as required by claim 1. See e.g., Appeal Brief, page 17, lines 3-5; page 18, lines 2-5. As urged for the anticipation rejection, Appellant stated that patentable weight must be given to it. Id., page 18, lines 7-10.

We agree with the examiner’s determination that Kosak in combination with the secondary references (Nikiforov and Yu) are sufficient to establish a case of prima facie obviousness. The primary reason for our concurrence is the teaching in Kosak of a DNA polymerase and primers present in a liposome or wax bead, commingled with other components of a primer extension or polymerase reaction. See e.g., Kosak, column 14, lines 35-60. The wax beads can be arrayed in a 96-well microtiter plates. Id., column 13, lines 24-27; column 28, lines 45-48. Kosak clearly discloses DNA and RNA polymerases entrapped in a liposome or wax bead (e.g., column 5, line 13-38) and then placed at distinct locations (e.g., column 13, lines 9-27) as required by claim 1 and others. (The primers are not covalently attached to the plate surface, but we have construed the claims not to require this.) Appellant’s contention is that Kosak do not describe a pulse-jet deposited polymerase. Brief, page 18. However, it is not necessary that the polymerase be pulsed-jetted into the array in order to satisfy the claim limitation.

To the extent that Kosak does not describe arrays of “at least two distinct primer compositions” or other individual limitations recited in the dependent claims, the

examiner has set forth adequate motivation to have complemented the deficiencies utilizing the teachings of Nikiforov, Yu, and/or Shipwash. See e.g., Examiner's Answer, pages 11 and 15. Essentially, Kosak teaches the broad application of their technology to nucleic acid reactions. Kosak, Abstract. Modifying Kosak to accomplish specific nucleic acid reactions is a routine matter of adapting this technology to other types of reactions as described in the additionally cited prior art references which would be well within the skill set of the ordinary skilled worker in the art. Appellant has not presented arguments to the contrary.

Because these references represent analogous art in the same technology field, the person or ordinary skill would reasonably be expected to look to them for the purpose of engaging Kosak's technology. In addition to the motivation-suggestion-teaching test, "a related test--the 'analogous art' test-- has long been part of the primary Graham analysis articulated by the Supreme Court. See Dann, 425 U.S. at 227-29, 96 S.Ct. 1393; Graham, 383 U.S. at 35, 86 S.Ct. 684. The analogous-art test requires that the Board show that a reference is either in the field of the applicant's endeavor or is reasonably pertinent to the problem with which the inventor was concerned in order to rely on that reference as a basis for rejection. In re Oetiker, 977 F.2d 1443, 1447 (Fed.Cir.1992)." In re Kahn, 441 F.3d 977, 986-987, 78 USPQ2d 1329, 1335-1336 (Fed. Cir. 2006).

Appellant provided no other basis to distinguish the claims over the cited prior art. Since Appellant did not argue that any of the claim limitations were not satisfied by the combination of cited references, we affirm the examiner's rejection with respect to claims 1-7, 12, 14, 17, 18, and 39 as being obvious over Kosak in view of Nikiforov;

claims 1-7, 12 and 14-16 as being obvious over Kosak in view of Yu; claim 13 as being obvious over Kosak in view of Nikiforov, and further in view of Shipwash; and claim 13 as being obvious over Kosak in view of Yu, and further in view of Shipwash.

Group II, claims 8-11 and 19-28

In the Brief, Appellant distinguished claims 8-11 and 19-28 (Group II) from the other claims in the application since these included the claim limitation that the array was “in a dry, storage stable format.” Appeal Brief, page 13. Although the limitation was present throughout prosecution, the examiner did not expressly address it, even though dependent claim 8 and independent claim 19 recited it. Not until the Appeal Brief was filed did Appellant first argue that the “dry, storage stable format” was absent from the prior art. In response to it, the examiner alleged that the “wax coated reagents [disclosed by Kosak] are a dry, stable storage format.” Answer, page 31, lines 5-10. Appellant dismissed this explanation, pointing to the specification where the claimed dry format was defined as “not being fluid compositions.” Reply Brief, paragraph spanning pages 7-8.

We agree with Appellant that the wax beads or particles described in Kosak are fluid, and therefore do not satisfy the claim limitation as alleged by the examiner. For example, the product is described as a “liquid heat-releasable reagent coated with a waxy polymer.” (Underlining added.) Id., column 12, lines 56-60. See, also column 2, line 65-column 3, line 1. Kosak also discloses a heat-releasable liposome which is defined as “a lipid bilayer membrane that completely encloses an aqueous space.” (Underlining added.) Id., column 7, lines 5-10. Reagents, including DNA polymerase and dNTP’s, can be entrapped within it. Id., column 9, lines 3-15. The description in

Kosak clearly covers beads and particles that are not dry, but which comprise an aqueous fluid component.

None of the cited secondary references make up for this clear deficiency. Yu is cited for its disclosure of dried arrays comprising oligonucleotide primers (e.g., ¶ 105), and the same can also be found in Ulfendahl (e.g., column 10, line 66). However, the claims include, in addition to the oligonucleotide primers, the polymerase enzyme and dNTPs. To establish obviousness, there must be some teaching, suggestion, or motivation to combine the references. In re Rouffet, 149 F.3d 1350, 1355-1356 (Fed. Cir. 1998). The examiner provided no motivation with expectation of success to have air-dried the polymerase and dNTPs, side-by-side with the oligonucleotide primers. Thus, we reverse the rejection as to claims 8-11 and 19-28. However, a new ground of rejection of these claims is set forth below pursuant to 37 C.F.R. § 41.50.

Group III, claims 29-38

Claims 29-38 (Group III) were separately argued by Appellant because they recite an active step in which a DNA polymerase and other DNA synthesis reagents are applied to a DNA primer array by pulse-jet deposition. Appeal Brief, page 21. In contrast to claims 1-28 which recited the limitation that the polymerase was a “pulse-jet deposited polymerase,” the Group III claims expressly require an active step of pulse-jet deposition.

Shipwash

Claims 29-38 were rejected under 35 U.S.C. § 103 as unpatentable over Kosak in view of Yu, and further in view of Shipwash.

As discussed previously, Shipwash discloses the use of jet-pulse technology to deliver samples and reagents to microwells. Shipwash, ¶ 179. The examiner argued that it would have been obvious to have applied this technology to deliver all the recited reagents in view of Shipwash's suggestion. In rebuttal, Appellant stated that Shipwash failed "to teach or suggest pulse jet-deposition of a polymerase," but failed to explain why motivation was lacking when it was admitted that this technology had been used to deliver protein reagents. Appeal Brief, page 21. Compare Specification, ¶ 5. Moreover, Appellant did not point out why it was not obvious to have used pulse-jet technology to deliver any of the other recited reagents.

In view of the admission that pulse-jet had been utilized for protein deposition, and Shipwash's express acknowledgement that it can be used in micro-array assays, we agree that the skilled worker would have been motivated with a reasonable expectation of success to have modified Kosak in view of Yu by utilizing pulse-jet technology to deliver certain reagents for the advantages described in Shipwash. Thus, we affirm the rejection of claims 29-38.

Church

Claims 29-38 were rejected under 35 U.S.C. §103 as unpatentable over Kosak in view of Yu and further in view of Church.

Beginning in ¶ 260 of the Church published patent application, a multiplex PCR method is described. The method utilizes microarrays of immobilized primers. Church, ¶ 262. It is stated in the Church disclosure at ¶ 263:

There are at least two ways primer pairs may be distributed. First, two presynthesized to Acrydite primers may be codeposited (Kenney et al., 1998, Biotechniques 25: 516-521; Rehman et al., 1999, Nucl. Acids. Res. 27: 649-655),

along with template and polymerase, in a gel volume element, for example by aerosol, emulsion, or inkjet printer, from an equimolar primer mixture.

According to the examiner, the “ordinary artisan” would have recognized the benefit of inkjet/pulse-jet deposition “to enable more rapid, automated and higher density array format,” providing the motivation to have utilized Church’s teaching to deposit the polymerase which is described in the assays of Kosak, Yu or Ulfendahl.

Appellant argued that Church’s example “does not teach pulse-jet deposition of polymerase but rather pulse-jet deposition of chemical reagents used in the synthesis of oligonucleotides.” Appeal Brief, page 22. To support their arguments, they referred to the Kenney and Rehman citations in ¶ 263 of Church, neither of which disclosed inkjet deposition of polymerase.

We agree with the examiner that Church discloses pulse-jet deposition of polymerase. This is expressly stated in plain language in ¶ 263 of Church. It is not significant that the cited Kenney and Rehman publications do not disclose deposition of polymerase since, from their position in the paragraph, it is more reasonable to conclude that their relevance was to the acrydite primer disclosure. (It is noted that these references were not provided, so an independent assessment of their content was not made.)

Appellant further argued that to the extent Church is found to disclose inkjet deposition, the reagents are in a gel volume, “not on a solid support as in the instant claims and thus polymerase is necessarily dispersed throughout the gel volume containing the array rather than at discrete locations on an array surface ...” Reply Brief, page 10.

To accept Appellant's argument, it would be necessary to construe the phrase "DNA primer compositions immobilized on a surface of a solid support" to exclude deposition into a gel on a solid support – the configuration described by Church. We decline to make this construction for two independent reasons. The gel described in the Church publication is present on the surface of a solid, such as glass. Church, ¶ 100. In this arrangement, the polymerase is immobilized on the glass, i.e., by being present in the gel which rests on the solid support. Our claim construction does not exclude this configuration, even if the gel itself is not a solid support. For instance, the examples in the specification include the deposition on to the solid support of the polymerase suspended in a fluid – analogous to how gel is deposited on the glass in the Church disclosure.

Secondly, the gel, itself, comprises a solid support. As defined in Church, a gel is a semi-solid with both solid and liquid components. *Id.*, ¶ 64, 82, 99. It is reasonable that the polymerase, when deposited into the gel, would be in contact with at least some of the solid components of the gel.

Appellant's statement that the polymerase is "necessarily dispersed throughout the array" is not persuasive since the deposition method, by their own admission, would result in it being located at discrete positions. To the extent that diffusion would occur in the matrix, resulting in the dispersion of the polymerase over time, the polymerase would be initially localized to a distinct location, and that is sufficient to meet the claim limitation. See, e.g., Exxon Chemical Patents v. Lubrizol Corp., 64 F.3d 1553, 1558,

35 USPQ2d 1801, 1804 (Fed. Cir. 1995) where a claim scope was construed as not to be time-limited, but to read on products that at any time contained the claimed proportion of ingredients.

Appellant's argument that it was uncertain that polymerases could be deposited by pulse-jet methods is also not credible. Appeal Brief, page 23. Notwithstanding the fact that Church, in fact, describe pulse-jet deposition for polymerase, in ¶ 5 of the application, it is admitted by Appellant that the use of pulse-jet to dispense proteins was known in the prior art. This would have led the skilled worker to reasonably expect that polymerases could be deposited by pulse-jet technology and still retain functional activity. The statement in ¶ 48 of the application that pulse-jet deposition "does not adversely affect the desired protein activity/functionality of the reagent of interest in the fluid" does not offset this expectation since the admitted prior art indicates that at least some activity levels would have been expected, and Appellant did not establish the actual levels were unexpected.

Thus, we affirm the rejection of claims 29-38.

6. New rejections

Two new rejections were set forth in the Examiner's Answer in which Church was combined with Yu, and also independently with Ulfendahl. Since we have affirmed rejections of most of the newly rejected claims for anticipation based on Yu or Ulfendahl, we find it unnecessary to address the merits of either of the new rejections. Claim 8 was included in the new rejections but not in the rejections for anticipation that we have affirmed; however, we enter a new rejection of claim 8 infra.

New Grounds of Rejection under 37 C.F.R. § 41.50

New grounds of rejection are set forth below over claims 8-11 and 19-28. The common feature of all these claims is the requirement that the array be in a “dry, storage stable format.” Although the dry, stable format is a key feature distinguishing dependent claim 8 and independent claim 19 from independent claims 1 and 29, only several lines (page 31) were devoted to it in the 43-page Answer. This feature was ignored until the appeal stage, indicating that proper attention to it had not been given during prosecution.

Claims 8 and 9

Pursuant to 37 C.F.R. § 41.50, a new ground of rejection is made for claims 8 and 9 under 35 U.S.C. § 103 as being obvious over Ulfendahl in view of Yu and Morozov⁸.

The disclosures of Ulfendahl and Yu have been discussed above and in the Examiner’s Answer. Ulfendahl describes arrays comprising DNA primers, polymerases, and precursor nucleotides, including dATP, dGTP, dTTP, and dCTP at distinct locations. See, e.g., Ulfendahl, Example 1, columns 6-8. At least one of the nucleotides is labeled (“FI-dCTP”). Id., column 7, line 46. Thus, the primer composition required in claim 8 is met. Divalent cations (magnesium) and buffering salts (Tris-HCl) are present as required by claim 9. Id., column 7, lines 60-65.

⁸ Morozov et al. (Morozov) U.S. Pat. No. 6,787,313, issued Sept. 7, 2004 (cited on PTO-892, attached to this decision)

Neither Ulfendahl nor Yu describe arrays comprising a polymerase in a dry, stable format as required by claim 8. However, Morozov describes dry protein or DNA arrays, including the use of trehalose to protect proteins against damage caused by drying. See e.g., Morozov, column 1, lines 19-25; column 16, line 30-column 17, line 11; column 27, Example 4. (See Specification, ¶¶ 56, 92, where the presence of trehalose is described in the specification as stabilizing the polymerase during the drying process). Since Morozov discloses dry protein and DNA arrays, and methods of making them (e.g., column 27, Example 4), the person of ordinary skill in the art would have been motivated with a reasonable expectation of success to have applied this technology to the array described in Ulfendahl for the purpose of producing kits comprising prefabricated dry DNA arrays as described in Yu (e.g., ¶¶ 76, 101). The application of Morozov's technology for drying arrays of protein and DNA would be well within the skill of the ordinary skilled worker.

Claims 8-11, 19, 20, and 24-28

Pursuant to 37 C.F.R. § 41.50, a new ground of rejection is made for claims 8-11, 19, 20, and 24-28 under 35 U.S.C. § 103 as being obvious over Yu in view of Ulfendahl and Morozov and Lin⁹.

The disclosures of Ulfendahl and Yu have been discussed above and in the Examiner's Answer.

⁹ Lin, U.S. Pat. No. 6,197,554, issued Mar. 6, 2001 (cited on PTO-892, attached to this decision)

Yu describes arrays comprising DNA primers, polymerases, and precursor nucleotides, including dATP, dGTP, dTTP, and dCTP at distinct locations. See, e.g., Yu, ¶ 106. At least one of the nucleotides (“Biotin 14-dCTP”) is labeled. Id. Divalent cations (magnesium) and buffering salts are also present. Id. Thus, these arrays contain the basic elements recited in claims 8, 9, and 19.

Yu state that reverse transcriptase can be utilized as a polymerase. Id., ¶ 37. This meets the requirements of claims 10 and 25. When a reverse transcriptase (RT) is utilized, Lin teaches that RNase inhibitors may be included in the reaction mixture for their well-known activity in protecting the RNA template copied by the RT. Lin, column 13, claim 31. The skilled worker would have been motivated to have included an RNase inhibitor in the DNA primer composition recited in claims 11 and 19 for its known purpose, as described by Lin, in protecting RNAs from degradation when using a reverse transcriptase.

Quantitative measurement of the nucleic acid analytes, as recited in claim 20 is disclosed by Yu at ¶ 1 and ¶ 64, and Ulfendahl at column 8, lines 24-29. The use of fluorescent labeled nucleotides as required in claim 24 is also disclosed by Yu. Yu, ¶ 42. Yu describes analysis of differential gene expression as recited in claim 26. Yu, ¶ 3-15, 64.

Ulfendahl describe a data transmission step to a remote location as required in claims 27 and 28, where data is collected from a TIRF instrument and then stored and analyzed in a spreadsheet. Answer, page 7. The skilled worker would have been motivated to have applied Ulfendahl’s method to Yu since such method is for analyzing the type of genetic information collected by Yu.

Neither Ulfendahl nor Yu describe arrays comprising a polymerase in a dry, stable format. However, Morozov describes dry protein or DNA arrays, including the use of trehalose to protect proteins against damage caused by drying. See e.g., Morozov, column 1, lines 19-25; column 16, line 30-column 17, line 11; column 27, Example 4. (See Specification, ¶¶ 56, 92, where the presence of trehalose is described in the specification as stabilizing the polymerase during the drying process). Since Morozov discloses dry protein and DNA arrays, and methods of making them (e.g., column 27, Example 4), the person of ordinary skill in the art would have been motivated with a reasonable expectation of success to have applied this technology to produce kits comprising prefabricated dry DNA arrays as described in Yu (e.g., ¶¶ 76, 101). The application of Morozov's technology for drying arrays of protein and DNA would be well within the skill of the ordinary skilled worker.

Claims 21-23

Pursuant to 37 C.F.R. § 41.50, a new ground of rejection is made for claims 21-23 under 35 U.S.C. § 103 as being obvious over Yu in view of Ulfendahl and Morozov and Lin as applied to claims 8-11, 19, 20, and 24-28, and further in view of Shipwash.

Claims 21-23 are directed to delivering sample volumes (claim 21) by pulse-jet fluid deposition (claim 22). As stated above, Shipwash describes pulse-jet technology to deliver samples and reagents to microwells for nucleic acid reactions (claim 23). Shipwash, ¶¶ 179. For the reasons which are already stated on page 17 above, we find this to have been obvious application of a known technology.

Summary

The rejection of claims 1-28 as indefinite under 35 U.S.C. § 112, second paragraph, is reversed.

The rejections of claims 1-7, 12-18, and 29-39 are affirmed as being unpatentable over prior art.

The rejections of claims 8-11 and 19-28 under §103 are reversed.

New grounds of rejection of claims 8-11 and 19-28 under §103 are made pursuant to 37 C.F.R. 41.50.

Regarding the affirmed rejection(s), 37 CFR § 41.52(a)(1) provides "[a]ppellant may file a single request for rehearing within two months from the date of the original decision of the Board."

In addition to affirming the examiner's rejection(s) of one or more claims, this decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the appellant elect to prosecute further before the examiner pursuant to 37 CFR § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the appellant elects prosecution before the examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

AFFIRMED-IN-PART/REVERSED-IN-PART, 37 CFR § 41.50(b)

Toni R. Scheiner)
Administrative Patent Judge)
)
)
) BOARD OF PATENT
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Administrative Patent Judge) APPEALS AND
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