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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARK A. AKESON,
DAVID W. DEAMER, SEICO BENNER,
WILLIAM B. DUNBAR, NOAH A. WILSON, KATHY LIEBERMAN,
ROBIN ABU-SHUMAYS, and NICHOLAS HURT¹

Appeal 2014-009828
Application 13/615,183
Technology Center 1600

Before DONALD E. ADAMS, FRANCISCO C. PRATS, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to methods of controlling the activity of an enzyme on a polynucleotide substrate. The Examiner rejected the claims for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

¹ Appellants state that the “real party in interest in this appeal is The Regents of the University of California, which is the owner of the application by virtue of assignment from the named inventors.” App. Br. 3.

STATEMENT OF THE CASE

The sole rejection before us for review is the Examiner's rejection of claims 1–12, under 35 U.S.C. § 103(a), for obviousness over Akeson,² Bhatnagar,³ and Nielsen.⁴ Final Action 5–10; Ans. 3–8.

Claim 1, the sole independent claim on appeal, illustrates the appealed subject matter and reads as follows (App. Br. 16):

1. A method for controlling the activity of an enzyme on a partially double-stranded polynucleotide complex, the method comprising:
 - (a) providing two separate, adjacent pools of a medium and an interface between the two pools, the interface having a channel so dimensioned as to allow passage from one pool to the other pool of only one single-stranded polynucleotide at a time;
 - (b) providing a partially double-stranded polynucleotide complex comprising a first polynucleotide, a second polynucleotide, and a blocking primer in one of the two pools;

wherein the blocking primer is bound to the partially double stranded polynucleotide complex and a portion of the blocking primer is incompatible with the second polynucleotide;

- (c) providing an enzyme having binding activity to the partially double-stranded polynucleotide complex in the

² Mark Akeson et al., US 2006/0063171 A1 (published Mar. 23, 2006).

³ Satish K. Bhatnagar et al., U.S. Patent No. 5,593,840 (issued Jan. 14, 1997).

⁴ Peter E. Nielsen and Michael Egholm, *An Introduction to Peptide Nucleic Acid*, 1 Curr. Iss. Mol. Biol. 89–104 (1999).

same pool as the partially double-stranded polynucleotide complex;

- (d) allowing the enzyme to bind to the partially double-stranded polynucleotide complex wherein the blocking primer prevents the activity of the enzyme on the partially double-stranded polynucleotide complex; and
- (e) applying a potential difference between the two pools, thereby creating a first polarity and removing the blocking primer; thereby controlling the activity of the enzyme on the partially double-stranded polynucleotide complex.

OBVIOUSNESS

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .

After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

In the instant case, the Examiner found that Akeson describes a process that differs from the process recited in claim 1 only in that Akeson does not expressly teach the use of a blocking primer. Ans. 4–5. The Examiner found, however, that an ordinary artisan would have considered it obvious to use a blocking primer, as taught in either Bhatnagar or Nielsen, in Akeson’s process, because Akeson described the use of a stalling reagent to inhibit the action of the polymerases used in its methods. *Id.* at 5–8.

Appellants argue, among other things, that in the embodiment shown in Akeson’s Figure 4, upon which the Examiner primarily relies, Akeson does not provide its polynucleotide-binding enzyme in the same pool as the

double-stranded polynucleotide complex, as required by claim 1. App. Br. 14–15. Appellants contend, moreover, that while the Examiner relies on Figure 6 of Akeson to teach combining the polynucleotide-binding enzyme and the double-stranded polynucleotide complex in the same pool, the embodiment shown in Figure 6 that has the polynucleotide-binding enzyme and the double-stranded polynucleotide complex in the same pool does not describe the use of a stalling reagent. *Id.* at 14–15; *see also* Reply Br. 6.

The Examiner responds that Akeson “teaches iterations of nanopore devices wherein the positioning polynucleotide/molecular motor complex resides in the same pool (see Figs. 6-7 & 9-10; paras. 0086-007 (ssDNA with primer bound on either cis or trans side), as examples).” Ans. 25. Furthermore, the Examiner contends:

[A] skilled artisan would have been motivated to place all components in the same pool in order to avoid the extra step of drawing components to the other side, which is accomplished with nucleotide-based stalling reagent (e.g. nucleotide analogue inhibitor or non-hydrolyzable NTP analogues, the positioning polynucleotide 54 may contain strand portions that stall the process, etc.) of AKESON and the similar blocking primers of Nielsen and BHATNAGAR. . . . Indeed, similar to nucleotide analogue inhibitors or non-hydrolyzable NTP analogues, a blocking primer also interacts with nucleic acid strands (such as the instant “polynucleotide”) to block or “stall” “motors” such as polymerases; therefore, all components *must* be in the same pool.

Id. (citation omitted) (emphasis added).

We find that Appellants have the better position. The Examiner relies on the embodiment shown in Akeson’s Figure 4 for the stalling reagent. *See* Ans. 4.

As Appellants contend, in the embodiment shown in Figure 4, the molecular motor 26 (which may be a polymerase) and the stalling reagent 52 are placed on the same or “cis” side of the nanopore-containing barrier 22, and the positioning polynucleotide 54 is placed on the opposite or “trans” side of the barrier. Akeson Figure 4A. Claim 1, in contrast to Figure 4 of Akeson, requires the polynucleotide-binding enzyme and the polynucleotide to be placed together in the same pool, i.e., in the “cis” side, as Appellants contend. Br. 16 (step (c)).

In operation, as shown in Akeson’s Figure 4B, an electrical current is applied to the device, causing the positioning polynucleotide 54 to be drawn into and partially through the nanopore 24, allowing the molecular motor/enzyme 26 and stalling reagent 52 (that are on the trans side as compared to the initial position of the positioning polynucleotide) to become bound to the polynucleotide, resulting in a complex 56a that is held in place in the nanopore, and also resulting in the desired positioning of the molecular motor/enzyme 26 next to the nanopore 24. Akeson ¶ 61. Once the molecular motor/enzyme 26 is correctly positioned, it is immobilized by the addition of a matrix material 28 to the trans side of the device. *Id.* at Fig. 4D; ¶ 62. The positioning polynucleotide 54 is then removed by switching the polarity of the current, and the immobilized enzyme-containing nanopore device may be used to analyze target polynucleotide. *Id.* at Fig. 4C; ¶ 62.

Thus, the embodiment in Akeson that relies on the use of a stalling agent requires the positioning polynucleotide to be drawn from one pool of medium, on one side of a barrier, partially through the nanopore to a separate pool of medium, on the other side of the barrier, to allow the polynucleotide-binding enzyme and stalling reagent to bind to the

positioning polynucleotide, thereby placing the enzyme in the correct orientation adjacent to the nanopore. Because Akeson's embodiment that uses the stalling reagent therefore *requires* the positioning polynucleotide to be drawn, at least partially, from one pool of medium to the other, the Examiner does not persuade us that an ordinary artisan would have been motivated to modify that embodiment "to avoid the extra step of drawing components to the other side." Ans. 25.

It might be true, as the Examiner contends, that Akeson describes embodiments in which the positioning polynucleotide and polynucleotide-binding enzyme are placed in the same pool of medium, on the same or "cis" side of the nanopore-containing barrier in Akeson's device. Ans. 25 (citing Akeson Figs. 6, 7, 9, 10; ¶¶ 86, 87). As Appellants contend, however (App. Br. 14–15; Reply Br. 5–6), and the Examiner does not dispute, none of those embodiments includes a stalling reagent. *See* Akeson Figs. 6, 7, 9, 10; *see also id.* at ¶¶ 70–72 (discussing method of fabricating nanopore device shown in Fig. 6); ¶¶ 73–75 (discussing method of fabricating nanopore device shown in Fig. 7); ¶¶ 85–89 (discussing method *using* nanopore device shown in Fig. 9); ¶ 88–91 (discussing method *using* nanopore device shown in Fig. 10).

The Supreme Court has explained that, to sustain an obviousness rejection, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Thus, even post-*KSR*, "[o]bviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under

examination.” *Unigene Laboratories, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011).

In the instant case, the Examiner has merely shown that each separate limitation is disclosed in the prior art. The Examiner does not provide any specific analysis or discussion of the embodiments shown in Figures 6, 7, 9, and 10 of Akeson, or their underlying disclosures, or how they compare to the process recited in Appellants’ claim 1. Nor does the Examiner explain with any particularity how or why an ordinary artisan would have modified the specific processes, having the specific features, described in those specific embodiments, to include the stalling reagent described in Akeson, or the blocking primers described in Bhatnagar and Nielsen. Accordingly, we are not persuaded that the Examiner has articulated a sufficiently specific rationale that explains why an ordinary artisan would have combined or modified the various teachings of the cited references to arrive at a process having all of the steps and features required by claim 1.

Therefore, for the reasons discussed, Appellants persuade us that the Examiner has not shown that the combination of Akeson, Bhatnagar, and Nielsen would have rendered obvious the process recited in Appellants’ claim 1. Accordingly, we reverse the Examiner’s rejection under 35 U.S.C. § 103(a) of that claim, and its dependents, over those references.

REVERSED