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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIFE TECHNOLOGIES CORPORATION
Requester, Cross-Appellant and Respondent

v.

454 LIFE SCIENCES CORPORATION
Patent Owner, Appellant, and Cross-Respondent

Appeal 2017-006630
Reexamination Control 95/001,765
Patent 8,012,690 B2[1]
Technology Center 3900

Before RICHARD M. LEBOVITZ, JEFFREY N. FREDMAN, and RAE LYNN P. GUEST, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON REQUEST FOR REHEARING

Patent Owner requests rehearing ("Req. Reh'g") under 37 C.F.R. § 41.79(a)(1) of the Decision under 37 C.F.R. § 41.77(f) entered July 21, 2017 ("41.77f Dec."). The 41.77f Decision is subsequent to a Decision entered May 27, 2015 ("Decision on Appeal" or "DOA") in which the

[1] US Patent 8,012,690 B2 is hereinafter referred to a "the '690 patent."

Examiner's determination not to adopt two rejections based on Holliger and two rejections based on Drmanac were reversed. 41.77f Dec. 2.

CLAIM INTERPRETATION

In the Decision on Appeal, the interpretation of the phrase "capture primer is coupled to the enrichment beads" was in dispute. DOA 7. This phrase appears in the fourth step of claim 1 which reads as follows (emphasis added):

> [4] attaching one or more of the beads of the first subset comprising the immobilized complementary copies to one or more enrichment beads, wherein the beads of the first subset are attached to the one or more enrichment beads by hybridizing a capture primer to a portion of one or more of the immobilized complementary nucleic acid molecules and the capture primer is coupled to the enrichment beads.

As explained in the Decision on Appeal, in the recited attaching step, beads containing the immobilized complementary nucleic acid are attached to enrichment beads by hybridizing them to a capture primer. The question is whether the capture primer is coupled to the enrichment beads before capturing the complementary nucleic acid, after capturing it, or both before and after. The Examiner interpreted the disputed phrase to mean that the capture primer is already coupled to the enrichment beads when the "hybridizing a capture primer to a portion of one or more of the immobilized complementary nucleic acid molecules" is carried out. RAN 6. Patent Owner argued that the Examiner erred and that the broadest reasonable construction of the disputed phrase "permits the enrichment capture primer to be coupled to or disposed on the enrichment bead either before or after the

act of hybridization of the enrichment primer to the amplified nucleic acid templates." Owner Appeal Br. 8.

The Decision on Appeal adopted the Examiner's interpretation because:

1) The claim language "is coupled" specified the condition of the capture primer during the claimed process, namely "is coupled to the enrichment beads," in contrast to language in other steps of the claim which explicitly specified when and how the act was accomplished by using a verb ("attaching," "hybridizing"). DOA 7–9;

2) When claim 1 was amended (it was originally numbered as claim 45 during prosecution of the '690 patent), Patent Owner stated that an element of a dependent claim (claim 50) was being added to it. DOA 10–11. This element of claim 50 required "hybridizing a capture primer disposed on the enrichment beads," indicating that the capture primer is disposed on the beads prior to capturing the immobilized complementary nucleic acid molecules – consistent with the Examiner's interpretation of the claim. *Id.* However, in making the amendment, Patent Owner did not use the exact language of the dependent claim, but rather added the current language that "the capture primer is coupled to the enrichment beads." *Id.* at 11. Nonetheless, because Patent Owner made the representation to the Examiner, when the amendment was made, that the claim incorporated the element of the primer disposed on the beads before hybridization, we gave weight to it as a reason to adopt the Examiner's interpretation of the claim. *Id.* at 11–12;

3) During the prosecution of the '690 patent, the Decision on Appeal found that the Examiner had construed the claim to mean that the primers are bound to the beads before hybridizing. DOA 12–13. Thus, Patent Owner was aware of the Examiner's reliance on this construction in finding the claims initially patentable.

In the Request for Rehearing, Patent Owner contends that this interpretation and the rejection under 35 U.S.C. § 314(a) based on the interpretation is improper, but did not identify a defect in the reasoning other than to reiterate arguments already made. Req. Reh'g 8–9.

REJECTIONS BASED ON HOLLIGER

The Examiner's determination that claims 1–9 are obvious based on Holliger in combination with O'Neill, Lundeberg, Vann, and/or Oliphant was affirmed in the 41.77f Decision. 41.77f Dec. 5, 14.

Patent Owner appears to reiterate arguments made in the Appeal Brief, without identifying "with particularity the points believed to have been misapprehended or overlooked in rendering the Board's opinion reflecting its decision" as required in a request for rehearing under 37 C.F.R. § 41.79(b)(1).

Patent Owner characterizes Holliger's method and then states:

> there is no teaching or suggestion in Holliger of any use of beads for an enrichment step and certainly no suggestion of the specific enrichment step recited by amended claim 1, where a capture primer is hybridized to a portion of the immobilized complementary nucleic acid molecules and coupled to enrichment beads.

Req. Reh'g 12.

Patent Owner further argues

> In the instant claims, removal of unreacted primer occurs when the emulsion is broken, which occurs before the attachment of enrichment primers and removal of "zero" beads -- this difference is clearly delineated in the methods of the instant invention, as the unreacted primers are washed away when the emulsion is broken in step 3 of claim 1 and the "zero" beads are isolated and removed in steps 5-7 of claim 1. Unlike in Holliger, in the instant methods, beads are not used to remove unreacted PCR primers.

Id. (emphasis added).

To begin, the claims do not positively recite a step in which unreacted PCR primer is "washed" away when the emulsion is broken as asserted by Patent Owner. Step [2] of claim 1 recites "amplifying" the template nucleic acid, but makes no mention of PCR primers to do so. Step [3] of claim 1 requires breaking the aqueous emulsion to release the beads, but makes no mention of removing unreacted PCR primer as Patent Owner contends it does in the Request (see above).

The amplified nucleic acid is immobilized to the beads in step [2] ("immobilized to the one or more beads") but the claim does not require how the immobilization is accomplished. In at least one embodiment described in the '690 patent, the immobilization is achieved through binding of the template nucleic acid to a primer or other oligonucleotide linked to the bead. '690 patent, col. 3, ll. 50–57; col. 5, ll. 13–21, 54–61.

Once PCR is accomplished and the emulsion droplets are broken in step [3], some beads will be attached to the amplified product and some will not, presumably because some droplets do not have products which were able to bind to the beads, e.g., if the products were not complementary to the

oligonucleotide attached to the bead, or, if no product was produced. While Patent Owner states that unreacted primer is removed, this statement is not consistent with the claim language because the only pertinent step recited in the claim is of breaking the emulsion droplets. Consequently, in fact, "unreacted primer" would be present in the broken emulsion, absent a positive step to remove it. Thus, Patent Owner's characterization of the claimed method does not appear to be consistent with the actual language of the claim.

It is true, as stated by Patent Owner, that Holliger does not teach an enrichment step in which enrichment beads are used to capture the beads containing the amplified nucleic acid and separate the capture beads from beads which do not have the amplified immobilized nucleic primer (the latter which Patent Owner identifies as "zero beads"). Req. Reh'g 12. However, the 41.77f Decision referenced the discussion in the Decision on Appeal discussing the factual basis for concluding why it would have been obvious to one of ordinary skill in the art to have utilized the enrichment beads of O'Neill, Lundeberg, Vann, or Oliphant to capture Holliger's beads. 41.77f Dec. 6, 10. Patent Owner did not identify a defect in these findings or conclusion. Patent Owner repeats the argument that none of O'Neill, Lundeberg, Vann, and Oliphant "are concerned with removing 'zero' beads from amplicon-bound beads, as required by the instant claims." Req. Reh'g 13. However, isolating the capture beads using enrichment beads as described in O'Neill, Lundeberg, Vann, and Oliphant would necessarily result in separating the capture beads from the zero beads which do not contain the product. Patent Owner did not adequately explain what is

deficient, and as pointed out in the 41.77f Decision, each of O'Neill, Lundeberg, Vann, and Oliphant describe utilizing enrichment beads – the same step which is claimed. 41.77f Dec. 12–13. Indeed, separating out the zero beads is *not* positively recited in the claim, but isolating enrichment *is* recited, and this step is described in each of O'Neill, Lundeberg, Vann, and Oliphant.

We do not agree with Patent Owner's statement that "in the instant methods, beads are not used to remove unreacted PCR primers" distinguishes the method from Holliger. Req. Reh'g 12 (reproduced above). The claimed method does not have a positive step of removing primer. The claimed method, in isolating the enrichment beads in step [5], would also serve to isolate the beads from unreacted primer. Holliger also uses the beads to isolate the amplified DNA. 41.77f Dec. 7–8; Holliger 76–77 (Example 25) ("PCR fragments from one single cell are transferred to a single bead. Beads are pooled, interrogated for presence of a certain mutation or allele using fluorescently labelled probes (as described for 'Digital PCR') and counted by FACS.")

In sum, we have considered Patent Owner's arguments, but they do not demonstrate any particular points that the Decision misapprehended or overlooked.

Claims 10–14 and 16–19

The Examiner's determination that claims 10–14 and 16–19 are obvious in view of Holliger and Vann was affirmed in the 41.77f Decision. 41.77f Dec. 13–14. With respect to this rejection, Patent Owner does not

identify any particular points misapprehended or overlooked in rendering the Board's opinion reflecting its decision as required in a request for rehearing under 37 C.F.R. § 41.79(b)(1). Patent Owner contends that Holliger's disclosure would not motivate the skilled worker to modify its method to have arrived at claim 10, but does not identify a defect in the reasoning set forth in the Decision on Appeal referenced in the 41.77 Decision for having modified it with Vann's teachings. *See* DOA 24–26 (referring to the claim charts provided by Requester).

REJECTIONS BASED ON DRMANAC

The Examiner's determination that claims 1–8 are obvious in view of Drmanac in combination with O'Neill, Lundeberg, Vann, and/or Oliphant was affirmed in the 41.77f Decision. 41.77f Dec. 15.

Patent Owner contends that "there is no teaching or suggestion in Drmanac of the formation of any amplicon carrying beads or of any methods of separating amplicon-carrying beads away from 'zero' beads, as required by the instant invention." Req. Reh'g 15–16.

This contention is not persuasive. Patent Owner denies that "amplicon-carrying beads" are taught by Drmanac, but fails to address the express findings in the 41.77f Decision that "Drmanac describes discrete particles ('DP'), such as beads, which carry copies of the same DNA fragment. Drmanac 7: 11–17" and that Drmanac's DPs carry the amplified fragments. 41.77f Dec. 15, 16. Patent Owner in this Request for Rehearing simplify fails to address the factual findings identified in the 41.77f Decision and subsequent conclusion of obviousness based on Drmanac.

Patent Owner reiterates the argument that Drmanac does not teach separating zero beads (Req. Reh'g 16) when no such finding was made by the Examiner nor in the two Board Decisions. Rather, O'Neill, Lundeberg, Vann, and Oliphant were relied upon for this feature of the claim. Again, Patent Owner simply reiterates its allegations made in the Appeal Brief about lack of motivation to utilized enrichment beads, without identifying a defect in the facts or reasoning relied upon in the Board Decisions. Patent Owner further argues that none of the cited secondary publications "cure" the deficiencies in Drmanac, but do not identify a specific error or misapprehension in the DOA (incorporated into the 41.77f Decision at 16) explaining the reasoning for applying these references to Drmanac's method. DOA 31–32.

Claims 10–14 and 16–19

Independent claim 10 comprises the following limitation:

> hybridizing a 3' end of one or more of the complementary nucleic acid molecules immobilized on the beads of the first subset to one or more second primers that are then disposed on one or more enrichment beads enabled for isolation under a selective condition thereby linking the enrichment beads to one or more of the beads of the first subset;
>
> extending the second primer hybridized to the 3' end of the one or more complementary nucleic acid molecules, wherein the extension enhances bonding between the second primer and the complementary nucleic acid molecules immobilized on the beads of the first subset applying the selective condition to isolate the one or more enrichment beads from the beads of the second subset; and

The Decision on Appeal explained how Vann describes the hybridizing and extending steps of claim 10 and why it would have been obvious to do so, namely, to label the captured DNA. DOA 28–29. The 41.77f Decision repeated this reasoning, and responded to Patent Owner's argument that "in Vann, the primer is attached to the bead before hybridization to the nucleic acid target sequence":

> The Examiner addressed this argument in the Determination, finding with supporting evidence that the reverse order described in the claim was conventional, namely, "hybridizing a biotinylated oligonucleotide to amplified DNA then attaching it to streptavidin coated beads, was known in the art." 41.77d Determination 5. Patent Owner does not respond to the Examiner's finding in its subsequent Comments.

41.77f Dec. 18.

In the Request for Rehearing, Patent Owner makes this same argument, but now with respect to Drmanac: "in Drmanac, the capture primer is hybridized to the immobilized amplicon prior to being coupled to the enrichment beads." Req. Reh'g 17. Patent Owner did not address the determination that reversing the order of steps was known in the art. Thus, whether Vann or Drmanac teach this variation is not dispositive because the ordinary skilled worker knew that the order could be predictably reversed, and the evidence shows that it had been reversed in relevant DNA purification methods (*see* Examiner's 41.77d Determination 5). The facts have not been disputed in this Request for Rehearing nor has Patent Owner identified any particular points misapprehended or overlooked.

Patent Owner again reiterates that none of the cited publications teach a reason the skilled artisan would have had to remove the zero beads from

the population. Req. Reh'g. 18. However, as already explained, the skilled worker would have had reason to use the enrichment bead approach to enrich for the amplification products (41.77f Dec. 6, 10, 12, 16) instead of simply separating them by spreading them on a surface, e.g., to remove DPs which do not have the target bound to them.

REHEARING DENIED

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