NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

IN RE: ADVANCED CELL DIAGNOSTICS, INC.,
Appellant

2023-1063

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. 17/012,394.

Decided: July 18, 2024

ANNE M. REYNOLDS, Casimir Jones, SC, Middleton, WI, argued for appellant. Also represented by JOHN MITCHELL JONES.

SARAH E. CRAVEN, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, argued for appellee Katherine K. Vidal. Also represented by KAKOLI CAPRIHAN, AMY J. NELSON, FARHEENA YASMEEN RASHEED.

Before PROST, SCHALL, and REYNA, *Circuit Judges*.

REYNA, *Circuit Judge*.

Advanced Cell Diagnostics, Inc. appeals a decision of the United States Patent Trial and Appeal Board sustaining the examiner's final rejection of certain claims of U.S.

Patent Application No. 17/012,394. ACD does not dispute that the prior art combination at issue discloses the limitations of the claims on appeal. Rather, ACD challenges the Board's motivation to combine and reasonable expectation of success findings, as well as the Board's consideration of two expert declarations. Because we determine that the Board's findings are supported by substantial evidence and that the Board did not err in its consideration of ACD's expert declarations, we affirm.

BACKGROUND

I. The '394 Application

Applicant Advanced Cell Diagnostics, Inc. ("ACD") filed U.S. Patent Application No. 17/012,394 ("'394 application") with the United States Patent and Trademark Office ("PTO"). The technology at issue relates to *in situ* hybridization, a known method of localizing and detecting specific nucleic acids *in situ,* i.e., in an intact cell. The '394 application describes a method for the detection of two or more nucleic acid targets using capture and label probes using *in situ* hybridization. Each capture probe in the claimed method has a "T section" and an "L section." The T section hybridizes with a section of the target nucleic acid while the L section hybridizes with a label probe.

As displayed below in Figure 4 of the application, the claimed system uses sets of capture probes, with each set comprising two separate capture probes, e.g., set 1 including probe L1-T1 and probe L2-T2. Each set of capture probes hybridizes to the target nucleic acid and to a label probe ("LP") that contains a detectable label, which is displayed as "SGP" below.

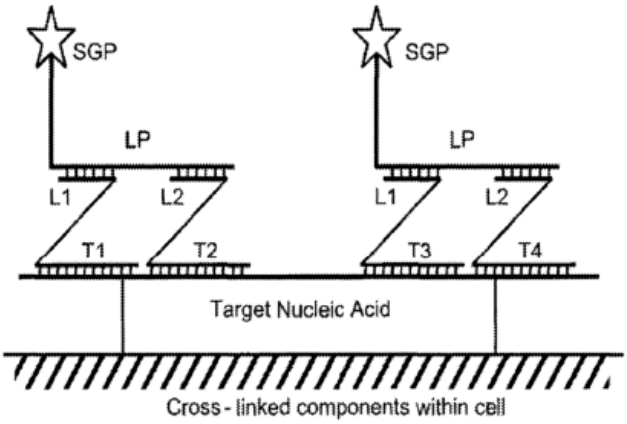

FIG. 4

'394 application, Fig. 4.

According to the application, one advantage of the claimed system is to increase stability and specificity of binding among all pieces of the system. Previously, linkage between a label probe and the target nucleic acid tended to be unstable and fall off when only one capture probe was in place. The claimed system, which uses multiple capture probes, results in "exceptional specificity because the signal-generating label probe can only be attached to the target gene of interest when two independent capture probes both recognize the target and bind to the adjacent sequences or in very close proximity of the target gene." J.A. 337, ¶ 202.

For purposes of this appeal, independent claim 98 of the '394 application is representative and recites in relevant part:

> 98. A method of detecting two or more nucleic acid targets within an individual cell, the method comprising:

providing a sample comprising the cell, which cell comprises or is suspected of comprising two or more nucleic acid targets;

providing for each nucleic acid target a label probe system comprising two or more identical label probe complexes, each of which comprises a nucleic acid component and one or more labels, wherein the labels of the label probe systems are distinct for each target nucleic acid;

providing for each nucleic acid target a capture probe system comprising two or more sets of capture probes, wherein each set of capture probes comprises two or more different capture probes, wherein all capture probes in the capture probe system comprise a T section and an L section, wherein the T section is a nucleic acid sequence complementary to a section on the nucleic acid target and the L section is a nucleic acid sequence complementary to a section on the nucleic acid component of the label probe complex, and wherein the T sections of the two or more different capture probes are complementary to non-overlapping regions of the nucleic acid target, and the L sections of the two or more different capture probes are complementary to nonoverlapping regions of the nucleic acid component of the label probe complex;

hybridizing, in the cell and in the presence of cellular non-target nucleic acids, the capture probe system to the two or more nucleic acid targets, when present in the cell, thereby providing hybridization of two or more different capture probe sets to a single copy of the nucleic acid target molecules in the presence of cellular non-target nucleic acids;

capturing, in the cell and in the presence of cellular non-target nucleic acids, the label probe system to the capture probe system hybridized to the nucleic

> acid target molecules, wherein the capturing occurs by simultaneously hybridizing the two or more different capture probes in each capture probe set to a single molecule of the nucleic acid component of the label probe complex that is complementary to the L sections of the two or more different capture probes, thereby capturing the two or more label probe complexes to the nucleic acid target in the presence of cellular non-target nucleic acids; and
>
> detecting a signal from the two or more label probe complexes captured on the nucleic acid targets, wherein the presence of a signal indicates the presence of the nucleic acid targets in the sample, and the absence of a signal indicates the absence of the nucleic acid targets in the sample.

'394 application, claim 98.

II. Prior Art

There are three prior art references at issue in this appeal: Kenny,[1] Urdea,[2] and Ward.[3] Kenny discloses a method of *in situ* detection of one target nucleic acid in a cell using T-L capture probes and a labeling system. Unlike the application at issue, Kenny does not teach using capture probe *sets* or detecting *multiple* nucleic acid targets.

Concerning the label probe system, Kenny discloses a preferred embodiment, which includes a branched network of probes that hybridize to a plurality of detectable label probes. Kenny alternatively notes that other label probe systems may work. Kenny discloses that once a capture probe is hybridized to the target nucleic acid, "*any method*

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1 WO 01/94632 A2, published Dec. 13, 2001.
2 U.S. Patent No. 5,681,697.
3 U.S. Patent No. 6,007,994.

that can detect [capture] probe complexes on the substrate may be used to determine the presence of the nucleic acid analyte." J.A. 751, 13:20–21 (emphasis added).

Urdea discloses an *in vitro* hybridization method. An *in vitro* environment is one where the target nucleic acids are separated from the cellular environment and interact with probe molecules tethered to a solid support.

Urdea additionally discloses hybridization using T-L capture probes that hybridize with a target nucleic acid and a label probe. Like the '394 application, Urdea teaches using sets of capture probes. According to Urdea, using sets of capture probes provides a detectable signal of only the target nucleic acid of interest and thus reduces "background noise" derived from non-specific hybridization and non-specific binding.

Finally, Ward discloses a hybridization method to detect multiple target nucleic acids. This process is referred to as "multiplexing."

III. Proceedings before the PTO

The examiner rejected independent claim 98 as obvious in view of Kenny, Urdea, and Ward. The examiner also rejected various dependent claims, which are not directly at issue in this appeal.[4]

In support of its application, ACD submitted the declarations of Dr. Mickey S. Urdea, a named co-inventor of Urdea, and Dr. Daryn Kenny, a named co-inventor of Kenny. Both declarants opined that at the time the application at issue was filed, a skilled artisan would not have

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[4] ACD does not separately challenge the rejections of any dependent claims and thus for this appeal, the following claims will rise or fall with independent claim 98: claims 99–104, 107, 108, 111–18, 120, and 121. Appellant Br. 3 n. 1.

had a reasonable expectation of success in combining Kenny, Urdea, and Ward. The examiner dismissed Dr. Urdea's testimony as "merely . . . the opinion of a someone [sic] compensated for the opinion" and contradicted by the record. J.A. 588. Similarly, the examiner dismissed Dr. Kenny's testimony as providing "only the paid declarants [sic] opinion, but no evidence." J.A. 593.

The Patent Trial and Appeal Board ("Board") affirmed the examiner's rejection of claim 98 as obvious over Kenny, Urdea, and Ward. The Board determined that these references teach all of the limitations of claim 98: (1) Kenny teaches an *in situ* hybridization method using capture probes to detect a target nucleic acid, (2) Urdea teaches using sets of capture probes, and (3) Ward teaches hybridization to two or more target nucleic acids (multiplexing). The Board also found a skilled artisan would be motivated to improve (1) Kenny's *in situ* hybridization method by using Urdea's capture probe sets and label probe system to increase specificity in detection of target nucleic acids and (2) the Kenny and Urdea combination with Ward's multiplexing system to allow for detection of multiple target nucleic acids. J.A. 12–13. The Board then found a reasonable expectation of success in arriving at the claimed invention because the three references were based on "decades old, basic nucleic acid hybridization technology" well known to skilled artisans at the time of ACD's claimed invention. J.A. 16 (emphasis removed).

In arriving at these findings, the Board rejected ACD's declarations from Drs. Urdea and Kenny as unpersuasive. The Board determined that these declarations failed to provide evidentiary support for the underlying opinions and contradicted the teachings of the references at issue. J.A. 17–20.

ACD appeals. We have jurisdiction under 35 U.S.C. § 141(a) and 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We "review Board decisions in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(2)." *HTC Corp. v. Cellular Commc'ns Equip., LLC*, 877 F.3d 1361, 1367 (Fed. Cir. 2017). Obviousness is a question of law with underlying factual findings relating to the scope and content of the prior art; differences between the prior art and the claims at issue; the level of ordinary skill in the pertinent art; the presence or absence of a motivation to combine or modify prior art with a reasonable expectation of success; and any objective indicia of non-obviousness. *Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373 (Fed. Cir. 2020). We review the Board's legal conclusions de novo and its factual findings for substantial evidence. *HTC Corp.*, 877 F.3d at 1367. Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938). We do not reweigh evidence on appeal. *Impax Labs. Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1382 (Fed. Cir. 2018).

On appeal, ACD challenges the Board's motivation to combine and reasonable expectation of success findings and the Board's consideration of the Urdea and Kenny declarations. We address each challenge in turn.

I. Motivation to Combine

ACD challenges the Board's motivation to combine determinations in three respects. For the following reasons, we reject ACD's challenges.

We first determine that the Board's motivation to combine findings are supported by substantial evidence, namely the references' teachings. Here, the Board first determined that a skilled artisan would have been motivated to improve Kenny's *in situ* method with Urdea's capture probe sets and label probe system for two reasons. First, the Board relied on the examiner's finding that a skilled

artisan would be motivated to combine the two because Urdea teaches the use of capture probe sets to decrease background noise and increase specificity. J.A. 12. Second, as the Board noted, a skilled artisan would be motivated to include Urdea's system in Kenny's because Kenny teaches that once the capture probes hybridize to the target nucleic acid, "any labeling probe or probe system . . . may be used to hybridize to the L portion of the T-L probe." J.A. 13 (citing Kenny's teachings at J.A. 751, 13:19–22, which provide that "*any method* that can detect the analyte-target probe complexes . . . may be used to determine the presence of the nucleic acid analyte" (emphasis added)).

The Board next determined that a skilled artisan would have been motivated to combine Kenny and Urdea's combined capture and label probe system with Ward because Ward's multiplexing process "would allow the detection of multiple sequences simultaneously." J.A. 13 (quoting the examiner's answer); *see also* J.A. 11 (citing Ward's teachings at J.A. 834, 2:55–60).

As the above shows, the Board rooted its motivation to combine findings in the teachings of the references themselves. We thus affirm the Board's motivation to combine findings as supported by substantial evidence.

Turning now to ACD's arguments to the contrary, ACD first argues that the Board misunderstood the teachings of Kenny and Urdea and thus, the Board's motivation to combine analysis was flawed. Appellant Br. 26. According to ACD, Kenny needed to be modified with an additional capture probe in order to arrive at the claimed capture probe set *before* it could be combined with Urdea's label probe system. *Id.* at 26–28, 41. ACD argues that the Board did not consider this modification when concluding that a skilled artisan would have been motivated to combine the two references. *Id.* at 28. Rather, according to ACD, the Board's combination of these two references resulted in a system that only had one capture probe hybridized to the

target nucleic acid, which does not meet the claimed capture probe set limitation.

The record, however, belies ACD's argument. The Board relied on the examiner's rejection when determining that a skilled artisan would be motivated to combine Kenny with Urdea. J.A. 12. As the rejection notes, and the Board found, a skilled artisan would have modified Kenny's one capture probe system "by use of *the two or more capture probe extenders hybridized* and labeling probe taught by Urdea in the in situ hybridization . . . method of Kenny." J.A. 12 (emphasis added) (quoting J.A. 678). Thus, the combination the Board relied on included two or more capture probes.

ACD next argues that even if the Board understood that Kenny must be modified to include a second capture probe, a skilled artisan would not be motivated to modify Kenny in that manner. Appellant Br. 28–32. According to ACD, Kenny's *in situ* environment has the potential to result in off-target binding given that "an abundance of native cellular structures and components are present in the samples, including off-target nucleic acids." *Id.* at 28–29. As such, ACD argues, a skilled artisan would expect that including an additional probe in Kenny would result in additional opportunities for off-target binding, reducing the chances of a successful detection of the target. *Id.* at 29.

Substantial evidence, however, supports the Board's finding that a skilled artisan would have combined Kenny with Urdea despite the differences in their assay environments. J.A. 15–17. The Board determined that (1) even *in situ*, Kenny discloses a method for capture probes reaching their intended targets *without non-specific binding to* cellular components and (2) ACD even recognized this point in its filings before the Board. J.A. 16–17 (citing J.A. 644, ACD's brief at 9). The Board also determined that, again based on Kenny's teachings, a skilled artisan would have understood how to make and use a probe that does not bind

non-specifically in an *in situ* method. J.A. 13 (citing Kenny, J.A. 751, 13:19–22); *see also* J.A. 15 (also citing Kenny, J.A. 751, 13:19–22). This is substantial evidence. ACD's arguments to the contrary are an invitation to reweigh evidence on appeal, which we cannot do. *Impax Labs.*, 893 F.3d at 1382.

Finally, ACD argues that the Board erred in finding a motivation to combine Ward with Kenny and Urdea. Appellant Br. 33–37. According to ACD, Ward teaches a more simplified probe system than those disclosed in Kenny or Urdea. *Id.* at 34. For this reason, and without fully explaining why, ACD argues that a skilled artisan would not be motivated to combine Ward's multiplexing system with the Kenny and Urdea combination. *Id.* at 35–37.

The Board's determination that a skilled artisan would be motivated to combine Ward with Kenny and Urdea is supported by substantial evidence. As previously discussed, the Board looked to Ward's teachings of its multiplexing system and concluded that based on this evidence, a skilled artisan would be motivated to include Ward's multiplexing system because it "would allow the detection of multiple sequences simultaneously." J.A. 13; *see also* J.A. 10. ACD's conclusory argument that Ward's simplified probe system somehow negates a motivation for achieving simultaneous detection of nucleic acid targets is a veiled invitation to reweigh evidence on appeal and thus fails. *Impax Labs.*, 893 F.3d at 1382.

II. Reasonable Expectation of Success

The Board determined that a skilled artisan would have had a reasonable expectation of success in combining the three references at issue. J.A. 12, 15–16. ACD argues that this finding was "entirely conclusory" and thus improper. Appellant Br. 32, 37–38. We disagree with ACD's argument.

"Evidence of a reasonable expectation of success, just like evidence of a motivation to combine, may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." *Elekta Ltd. v. ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1377 (Fed. Cir. 2023) (citations and internal quotation marks omitted). Here, the Board first found a skilled artisan would have reasonably expected Urdea's label probe system and capture probe sets to reach their intended targets even in Kenny's *in situ* environment. *See* J.A. 15 (citing Kenny's teachings at J.A. 751, 13:19–22). Second, the Board found, based on Kenny's teachings, that a skilled artisan would have understood how to make and use a probe that does not bind non-specifically in an *in situ* method. J.A. 15 (citing Kenny's teachings at J.A. 751, 13:19–20). Finally, the Board found that a skilled artisan would have reasonably expected success in combining Kenny and Urdea with Ward because such combination was based on "decades old, *basic nucleic acid hybridization technology*" that was well known in the art. J.A. 16 (emphasis in the original). The teachings of the three prior art references, the nature of the technology at issue, and the knowledge of one of ordinary skill in the art are sufficient evidence to support the Board's reasonable expectation of success findings.

Moreover, we determine that the evidence supporting the Board's motivation to combine findings also support its reasonable expectation of success findings. Here, ACD's reasonable expectation of success arguments are largely duplicative of its motivation to combine arguments. *Compare* Appellant Br. 26–32, 33–37 (motivation to combine arguments) *with id.* 32–33, 37–38 (reasonable expectation of success arguments); Oral Arg. 2:27–2:54, 10:50–11:03. In some cases, when the arguments of reasonable expectation of success are the same for motivation to combine, the evidence establishing the latter may establish the former. *Elekta*, 81 F.4th at 1377. This is the case here.

We affirm the Board's reasonable expectation of success findings.

III. Expert Declarations

Finally, ACD argues that the Board's decision is flawed because it gave "insufficient consideration" to the Urdea and Kenny declarations. Appellant Br. 38. The record, however, shows otherwise. The Board sufficiently considered the two declarations and determined that they lacked evidentiary support and ran counter to the teachings of the three references at issue. J.A. 17–19. On these bases, the Board determined the declarations were not persuasive. *Id.* We see no error in this determination.

ACD argues that even if the Urdea and Kenny declarations did not support the opinions expressed therein with supporting evidence, the Board should have nonetheless given the declarations "unique weight because they come from named inventors of the references themselves." Appellant Br. 45. ACD relies on *In re Oelrich*, 579 F.2d 86 (CCPA 1978), as support for this proposition.

We reject ACD's argument for two reasons. First, ACD's position overlooks well-established precedent. "The Board has broad discretion as to the weight to give to declarations offered in the course of prosecution." *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004). "[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations." *Id.* Indeed, a lack of factual support for expert opinion going to factual determinations may render the testimony of little probative value in a patentability determination. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985); *see also Velander v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003). That is what happened here. The Board determined that the Urdea and Kenny declarations lacked evidentiary support for the underlying positions and for this reason, deemed

them unpersuasive. We see no abuse of discretion with this determination.

Second, ACD's position is unsupported by the law. To hold that the Board *must* afford "unique weight" to unsupported expert declarations solely because the expert was a listed inventor of the prior art would result in a newfound deference to expert declarations in prosecution proceedings. We decline to create such a rule today.

Contrary to ACD's position, *In re Oelrich* does not support the creation of this new level of deference. In *In re Oelrich*, the United States Court of Customs and Patent Appeals ("CCPA"), this court's predecessor, determined that the Board's criticism of four affidavits was unwarranted. 579 F.2d at 91. The CCPA recognized that the affidavits reflected the opinions of skilled artisans with unique competence. *Id.* However, the CCPA further explained that the affidavits were based on facts or on "technically sound applications of unquestioned physical principles." *Id.* Thus taken as a whole, the CCPA determined that the affidavits' conclusions were reasonable and credible. *Id.* Although ACD would argue otherwise, this determination did not create a level of automatic deference to skilled artisans based solely on their status as named inventors. And in any event, unlike in *In re Oelrich*, the Board here determined that the Urdea and Kenny declarations were not supported by facts or unquestioned physical principles. Thus, *In re Oelrich* is readily distinguishable from this case.

In sum, we see no error in the Board's consideration of ACD's expert declarations.

CONCLUSION

We have considered ACD's other arguments and find them unpersuasive. For the reasons stated above, we affirm the Board's determination upholding the examiner's

rejection of claims 98, 99–104, 107, 108, 111–18, 120, and 121 as obvious.

AFFIRMED

COSTS

No costs.