

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIO BIOSCIENCE, INC.,
Petitioner,

v.

PROGNOSYS BIOSCIENCES INC.,
Patent Owner.

IPR2024-01289
Patent No. 10,480,022

**PETITIONER'S REQUEST FOR REHEARING OF THE BOARD'S
DECISION DENYING INSTITUTION (PAPER NO. 10)**

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Patent Trial and Appeal Board
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I. Introduction

Curio Bioscience, Inc. (“Petitioner”) respectfully requests rehearing of the Board’s decision Denying Institution of *Inter Partes* Review of the ’022 patent. *See* Paper 10 (the “Decision”). The Board abused its discretion in denying institution based on clearly erroneous factfinding and legal error at least with respect to Ground 2.

There, the Board concluded that “Armani [] fails to disclose determining a spatial location of the nucleic acids within a tissue sample because the sample itself is lysed and therefore fails to retain the spatial information of the sample nucleic acids within the tissue sample.” Decision at 24. This is a simple misapprehension of Armani, as there is no dispute that Armani discloses techniques that determine the spatial location of a nucleic acid in a tissue sample. The Board’s characterization of Armani is contradicted by the specification of the ’022 patent itself, which observed that “Certain PCR assays in a 2D format *preserve spatial information (see Armani, et al., Lab on a Chip, 9(24): 3526-34 (2009)).*” EX1001 at 1:50-56; Pet. at 62.

The Board’s analysis was also based on two erroneous conclusions of law. First, it relied on an implicit and unstated claim construction that added an additional “no lysing” limitation not found in the claims. Second, the Board rejected an obviousness ground based on anticipation reasoning by focusing its analysis on features allegedly missing from Cantor, rather than considering the prior art

modifications presented by the Petition.

This request is important. Petitioner is an early-stage company in the nascent spatial transcriptomics market, and Patent Owner is seeking to enjoin Petitioner's primary product lines in parallel district court proceedings. The PTAB is supposed to offer an efficient venue for Petitioner to quickly resolve baseless patent infringement claims based on invalid patents. It is thus critical that the Board address the Petition (and four related Petitions on which the Board has yet to render decisions) carefully based on an accurate understanding of the prior art and proposed grounds.

II. Legal Standard

The Board reviews a non-institution decision for an abuse of discretion. 37 C.F.R. § 42.71(c). "An abuse of discretion is found if [a] decision: (1) is clearly unreasonable, arbitrary, or fanciful; (2) ***is based on an erroneous conclusion of law***; (3) ***rests on clearly erroneous fact finding***; or (4) involves a record that contains no evidence on which the Board could rationally base its decision." *Intelligent BioSys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (internal citations omitted).

Misapprehending or overlooking a significant fact or argument constitutes clearly erroneous fact finding, and thus an abuse of discretion. *See Merial Ltd. v. Virbac*, IPR2014-01279, Paper 18 at 8 (P.T.A.B. Apr. 15, 2015). Abuse of discretion

based on an erroneous conclusion of law is found in situations such as when the Board adopts erroneous and unexplained implicit claim constructions, *PLR Worldwide Sales Ltd., v. FLIP Phone Games Inc.*, IPR2024-00133, Paper 12 at 6-7 (Aug. 22, 2024), and when the Board fails to adequately address arguments in the petition. *See Nokia of Am. Corp. v. Soto*, IPR2023-00680, Paper 18 (Mar. 28, 2024) (vacating decision denying institution).

III. Brief Summary of the Board's Errors

The claims of the '022 patent are directed to assays that involve “(b) contacting [a] plurality of beads with [a] tissue sample such that the binding agent interacts with the biological molecule” and “(c) . . . determining a spatial location of the biological molecule of the tissue sample.” EX1001, cl. 1. The claims do not specify or limit how the “contacting” occurs, nor do they require that the “determining” step occurs *within* the tissue sample.

The following passage of the Decision encapsulates the Board's errors:

Specifically, while Armani uses tissue as the nucleic acid source, the nucleic acid source “is lysed to release genomic DNA into solution.” [POPR] at 50. Thus, the combination of Cantor and Armani likewise fails to disclose determining a spatial location of the nucleic acids within a tissue because the sample itself is lysed and therefore fails to retain the spatial information of the sample nucleic acids within the tissue sample.

Decision at 24.

First, the Board's analysis is based on the factual misapprehension that "because the sample itself is lysed" the method of Cantor and Armani cannot be used to "determine a spatial location of the biological molecule of the tissue sample." *Id.* This contradicts the teachings of Armani, which explains that its methods "yield[] a molecular map that directly correlates with the histology of the sample." Pet. at 17. Further illustrating the Board's misapprehension that Armani "fails to retain the spatial information" due to lysing, the '022 patent itself admits the opposite: that Armani discloses a PCR assay that "***preserve[s] spatial information (see Armani, et al., Lab on a Chip, 9(24): 3526-34 (2009))***"; EX1001 at 1:50-56; Pet. at 62; EX1100, ¶84.

Second, the Board committed legal error by carrying out an implicit claim construction to add additional limitations not found in the claims, by requiring the combination to "retain the spatial information of the sample nucleic acids within the tissue sample," and excluding methods in which the tissue sample is processed, for example by lysis. Decision at 24. But nothing in the claims or specification supports (or enables) this narrow reading.

Finally, the Board committed another legal error by concluding that "Cantor says nothing about placing beads in a 'known location' on a substrate," *id.* (quoting POPR at 41), and therefore failing to consider the prior art as modified and presented in the Petition in its obviousness analysis. The Federal Circuit is clear that relying

on what the original reference allegedly fails to disclose in rejecting an obviousness argument amounts to “a conflation between the relevant standards for obviousness and anticipation.” *Honeywell Int’l Inc. v. 3G Licensing, S.A.*, 124 F.4th 1345, 1355 (Fed. Cir. 2025).

IV. Argument

In the Decision, the Board abused its discretion due to erroneous fact finding by concluding that the step of lysing a tissue sample in the combination of Cantor and Armani precluded the combination from rendering obvious the step of “determining a spatial location of a nucleic acid in a tissue.” The Board’s factual misapprehension was further compounded by two legal errors: (i) implicitly construing the claims by requiring the retention of spatial information “within the tissue sample,” thereby excluding methods involving lysis; and (ii) failing to consider, in an obviousness ground, the prior art as modified and presented in the Petition. Decision at 24.

A. Review of Ground 2

Ground 2 of the Petition set forth the theory that the combination of Cantor and Armani renders the challenged claims obvious when read in light of the knowledge of a POSA. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (obviousness analysis must take into account “the background knowledge possessed by a person having ordinary skill in the art . . . in order to determine whether there

was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.”). Specifically, Ground 2 incorporated Ground 1’s analysis. Ground 1 established that Cantor discloses nucleic acid binding arrays that provide “a plurality of beads with the claimed ‘binding agents’ in the form of nucleic acid constructs that include a ‘probe sequence’ that is ‘configured to interact’ with a target nucleic acid, as well as a ‘coding identifier’ or identification sequence’ that may be used to identify the specific bead, and thus location, at which a particular binding interaction occurred.” Pet. at 49. There is no dispute that Cantor discloses each physical element.¹ Ground 2 further relied on a specific embodiment of Cantor, in which the beads are arranged on “substrates having multiple wells or pits,” thereby “providing a plurality of beads containing the claimed binding agents by arranging the beads in a multiple well plate.” Pet. at. 50. This arrangement is expressly contemplated by dependent claim 3 of the ’022 patent, which recites “the plurality of beads is provided in wells on the substrate surface.” *Id.*

¹ As explained further in Section IV.D, to the extent the Board found that Cantor does not disclose correlating Cantor’s identification sequences to the location of a bead in an array because it does not expressly disclose a spatial component, this was a legal error because it failed to account for the Petition’s obviousness theory.

Armani discloses methods for determining the spatial location of a nucleic acid in a tissue section, in which (1) “the tissue section is transferred onto the surface of [a] multi-well array (step 1A) and then pressed onto the surface (1B),” after which (2) “the tissue is lysed to release genomic DNA into solution,” (3) the “DNA is

amplified” using PCR; and (4) “the DNA is imaged” using fluorescence detection. Pet. 50-51 (discussing EX1022 (“Armani”) at 3527). Because each subsection of the tissue sample is lysed and analyzed at a distinct region on the substrate (i.e., in a particular well), Armani discloses determining the location of a nucleic acid in a tissue sample because the presence of fluorescence in a given well indicates

that the nucleic acid was present at that location of the tissue sample. *Id.* (“2D-PCR[] makes use of a miniature array of wells together with protocols that allow *tissue lysis, DNA amplification, and target detection, within the same well.*”); EX1100, ¶¶80-84.

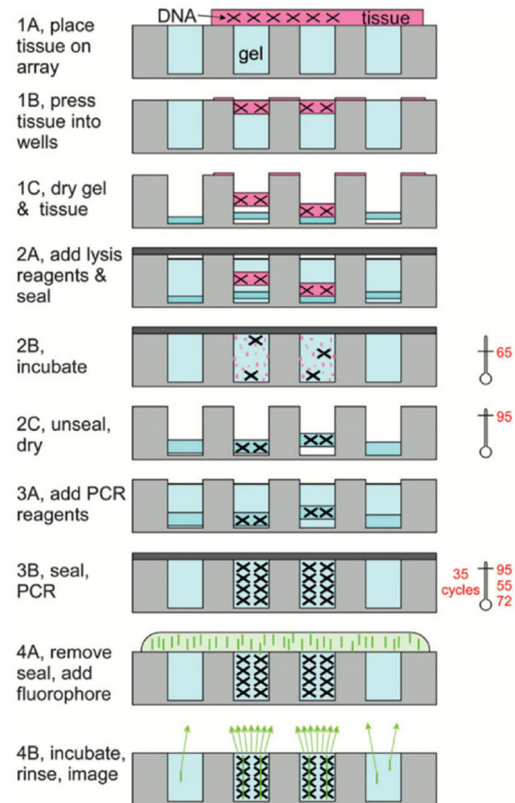


Fig. 2 Experimental protocol used to demonstrate the 2D-PCR concept. Tissue is transferred into wells, isolated, and lysed to extract the genomic DNA (represented by “x”s). PCR is performed to amplify the target DNA, and the targets are visualized with fluorescent dye (indicated by vertical lines “|”).

As a result, the '022 patent unambiguously admits that Armani discloses “Certain PCR assays in 2d format [that] *preserve spatial information*.” EX1001, 1:50-56. While the '022 patent criticizes Armani’s methods as having “low spatial resolution because they rely on physical transference [i.e., pressing] of tissue into wells,” there are no claim limitations requiring a particular level of spatial resolution. EX1100, ¶84.

The Petition explained that a POSA would have been motivated to combine Cantor’s bead-array-based nucleic acid binding, amplification, and identification techniques, including specifically Cantor’s microwell embodiment, with Armani’s microwell-based nucleic acid amplification techniques for spatial analysis of nucleic acids in tissue sections for several reasons. Pet. at 52-53. Specifically, while Armani discloses techniques for the spatial analysis of nucleic acids in a tissue section by using “visualization (e.g., fluorescence)” as a detection method, a POSA would have been motivated to use Cantor’s sequencing techniques for detection instead of Armani’s fluorescence-based PCR techniques to simplify the workflow and facilitate the analysis of mRNA. Pet. at 52-53.

B. The Board misapprehended Armani by concluding that it does not teach determining the location of a nucleic acid in a tissue sample.

The Board’s analysis is based on the factual misapprehension that “because the sample itself is lysed,” the method of Cantor and Armani cannot be used to

“determine a spatial location of the biological molecule of the tissue sample.”

Decision at 18, 24. On the contrary, according to the proposed combination, a tissue sample is placed on an array of microwells and subsections of that tissue sample are pressed into the individual microwells occupying the same spatial location, thereby preserving the spatial arrangement of the subsections of the tissue sample. The tissue segments are then lysed within the individual microwells they were pressed into, preserving the spatial arrangement of the nucleic acids in the tissue samples. Sequencing the nucleic acids in each of the microwells of the array retains and provides spatial information—i.e., it provides information on the location of the nucleic acids in the tissue sample. This is confirmed by the patent’s admission that Armani discloses a PCR assay that “*preserve[s] spatial information (see Armani, et al., Lab on a Chip, 9(24): 3526-34 (2009))*”; EX1001 at 1:50-56; Pet. at 62; EX1100, ¶84.

Armani’s physical transference is depicted in Figures 1 and 2, which illustrate the preservation of spatial information by transferring subsections of the tissue samples into microwells that are positioned at locations corresponding to the structure of the tissue slice. Figure 2 (reproduced above) depicts the process: starting from the intact tissue slice (1A), segments of the tissue are pressed into wells that correspond with the physical location of the tissue on the array (1B). Pet. at 50-51; EX1100, ¶238. The tissue sample is subjected to lysis reagents (2A-2C) in the well

into which it was transferred, before being subjected to PCR (3A-3B), and fluorescence imaging (4A-4B), again within the same well. Pet. at 50-51; EX1100, ¶238. This allows the creation of a detection map, because the microwell in which a nucleic acid was detected corresponds to the location at which it existed in the tissue sample. Pet. at 17; EX1022, Fig. 1.

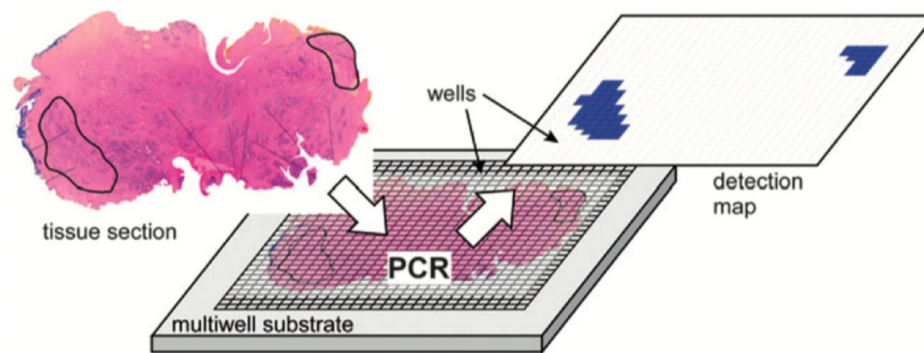


Fig. 1 2D-PCR is achieved by transferring a tissue section vertically into a multi-well array device, isolating tissue subregions. The DNA is extracted and then amplified by the polymerase chain reaction. A detection map is created by imaging the amplified DNA, for example using a DNA-intercalating dye.

The fact that the tissue sample is lysed to facilitate the amplification and detection of sample nucleic acid does not preclude the mapping of the presence of the sample nucleic acid to a location in the array. On the contrary, it facilitates determining the spatial location of the nucleic acids in the tissue sample, as illustrated by the detection map in Figure 1. *See* EX1022 at 3257 (“The 2D-PCR concept is illustrated in Fig. 1. A tissue is sectioned and transferred into a multi-well array device. The DNA is then extracted from the tissue and subsequently amplified

by PCR in the same wells. This method allows mapping of genes...). Hence, Armani unambiguously contradicts the Board's conclusion that it "fails to disclose determining a spatial location of the nucleic acids within a tissue because the sample itself is lysed and therefore fails to retain the spatial information of the sample nucleic acids within the tissue sample." Decision at 24.

C. The Board improperly engaged in claim construction by requiring nucleic acid analysis to occur on the tissue sample without lysis.

The Board's factual misapprehension of Armani was further compounded by the Board's implicit claim construction. Even though the parties did not raise any claim construction disputes, Decision at 8, the Board appears to have imported into the claims a requirement that the claimed methods be performed directly on the tissue sample, without modification or processing of the tissue. Decision at 24. By so doing, the Board abused its discretion. *See e.g., PLR Worldwide*, IPR2024-00133, Paper 12 at 7 (finding abuse of discretion and granting director review where Board did not expressly construe any claim terms but implicitly added limitations).

The Board provided no explanation as to why it read this requirement into the claims of the '022 patent. *See* Decision at 24. If the Board wanted to construe the claims, it should have "first assess[ed] the intrinsic evidence, and then consult[ed] extrinsic evidence if necessary." *PLR Worldwide*, IPR2024-00133, Paper 12 at 7. At a minimum, the Board legally erred by failing to provide any such explanation. *See*

Straight Path IP Grp., Inc. v. Sipnet EU S.R.O., 806 F.3d 1356, 1361-62 (Fed. Cir. 2015) (overturning Board decision that construed a term to contradict the plain meaning because “[t]he Board did not rely on any other basis for its construction”).

The Board’s implicit construction is also contradicted by the record. Importantly, Patent Owner has read the claims to encompass methods in which the tissue sample is lysed before determining the spatial location of a nucleic acid in the sample for purposes of infringement. EX1007. As a result, the Board’s implicit construction, which precludes such methods from rendering the claims obvious, cannot simultaneously be correct and consistent with Patent Owner’s infringement theory. *See* Pet. at 20 (“The Petition applies the understanding of the claim terms applied by PO to assert infringement against Curio.”).

Specifically, Patent Owner contends that Petitioner’s products satisfy step 1(c) of the ’022 patent, even though “the tissue is digested [i.e. lysed] before taking the beads through second strand synthesis and cDNA amplification,” which occurs before “[t]he determined sequences of the bead barcode and the mRNA are used to determine the spatial location of the biological molecule (mRNA) of the tissue sample.” EX1007 at 6-8 (excerpted and annotated below).

EXEMPLARY INFRINGEMENT CLAIM CHART
U.S. PATENT NO. 10,480,022

Claim Limitation	Curio Infringement
	Curio Bioscience, <i>Introducing Curio Seeker: High-resolution spatial transcriptomics</i> (March 1, 2023), https://www.youtube.com/watch?v=Kh-qYiu48, at 0:56-1:02. Next, the tissue is digested before taking the beads through second strand synthesis and cDNA amplification:  Curio Bioscience, <i>Introducing Curio Seeker: High-resolution spatial transcriptomics</i> (March 1, 2023), https://www.youtube.com/watch?v=Kh-qYiu48, at 1:03-1:10. The sequencing libraries are then prepared and sequenced; sequencing determines the sequence of the coding identifier (bead barcode) and the sequence of the captured mRNA:

D. The Board legally erred by failing to consider Cantor according to the Grounds presented in the Petition.

The Decision further erred in failing to consider Cantor from the perspective of a POSA. In a single parenthetical, the Board concludes that “Cantor says nothing about placing beads in a ‘known location’ on a substrate because Cantor’s beads contact a sample nucleic acid, which itself has no spatial information.” Decision at 24.

This conclusion cannot be squared with Cantor itself, or the interpretation of Cantor presented by the Petition. Notably, the Board “recognize[d] that Cantor discloses ‘providing the beads according to an (X,Y) array.’” Decision at 21. And as the Petition explained, Cantor discloses thereby “providing a plurality of beads containing the claimed binding agents by arranging the beads in a multiple well

plate.” Pet. at. 50. As the Decision acknowledges, there was no dispute that the level of skill in the art was high, and that the POSA would have had, among other skills, “a working knowledge of nucleic acid arrays [and] combinatorial chemistry techniques for making and using such arrays.” Decision at 8-9. Accordingly, Dr. Puglisi explained in extensive detail the array fabrication techniques that would have been well-known and obvious options to a POSA fabricating Cantor’s embodiment with beads arranged in a multi-well plate: (i) selective loading of particular beads to particular locations on the array; and (ii) randomly depositing the beads on the array followed by decoding. Pet. at 39-42; EX1100, ¶¶165-173 (citing, *inter alia*, EX1032 (Chee-584), 7:30-33 (“beads are spatially arranged ‘in a regular pattern of sites such that the sites may be addressed in the X-Y coordinate plane.’”); EX1038 (Chee-824); *see also* EX1038, [0013], [0043] (describing in 2007 publication, “positional decoding” of bead arrays by “targeting the placement of beads” to specified locations, or “selective loading of the sites” by disposing beads at particular locations in the array); *see also* EX1100, ¶¶65-70, 90.

By adopting Patent Owner’s contention that “Cantor says nothing about placing beads in a ‘known location,’” POPR at 41; Decision at 24, the Board improperly focused on the express teachings of Cantor alone, rather than the modifications motivated by the prior art and presented in the Petition. *Cf.* Pet. at 53; EX1100, ¶242 (explaining that Armani expressly motivates using Cantor’s

“identification probes to identify the location at which beads were provided” in the microwell devices disclosed in Cantor and Armani).

This was an abuse of discretion. The Federal Circuit is clear that relying on what the original reference allegedly fails to disclose in rejecting an obviousness argument amounts to “a conflation between the relevant standards for obviousness and anticipation.” *Honeywell*, 124 F.4th at 1355. In *Honeywell*, the Federal Circuit noted that when, as here, Petitioner puts forth an obviousness theory that accounts for the allegedly missing limitations in a prior art reference, “[i]n according *any* weight to the mere fact that there is a difference in the [] reference and [challenged] patent, the Board commit[s] legal error by ‘deviating impermissibly from the invalidity theory set forth in the petition.’” *Id.* (quoting *M&K Holdings, Inc. v. Samsung Elecs. Co., Ltd.*, 985 F.3d 1376, 1385 (Fed. Cir. 2021) (emphasis in original); see also *Qualcomm Inc. v. Intel Corp.*, No. 2022-1824, 2024 WL 4258364, at *2-3 (Fed. Cir. Sept. 23, 2024) (affirming the Board’s determination that the challenged claims were obvious over a single reference and that the “necessary modifications” within the knowledge of a POSA met the claims).

V. Conclusion

The Board should institute IPR.

Dated: April 9, 2025

Respectfully submitted,

/Andrew E. Krause/

IPR2024-001289

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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. § 42.6, that on April 9, 2025, a complete copy of the foregoing document, **PETITIONER'S REQUEST FOR REHEARING**, was served by ELECTRONIC MAIL, as agreed to by the parties, upon the following:

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