

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.,
Petitioner

v.

NANOSTRING TECHNOLOGIES, INC.,
Patent Owner

Case IPR2023-01300
U.S. Patent No. 11,473,142

PETITIONER'S PRE-INSTITUTION REPLY

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Petitioner files this pre-institution Reply as authorized by the Board.

EX3001. Patent Owner (“PO”) argues that neither Stahl nor So-456 teaches the sequencing step¹ or synthesis steps of claim 1 of the 142 patent. POPR, 4, 15-38.

However, as explained below, PO’s arguments—which are bare attorney arguments not supported by expert testimony²—are inconsistent with its litigation positions and should be rejected. EX1022, 18-20, 22-24. As the Petition demonstrated, both Stahl and So-456 teach these claimed steps under PO’s litigation claim interpretations. Pet., 22, 23, 26-31, 44, 56, 61-67, 77; EX1022.

I. The POPR’s argument regarding claim 1’s sequencing step (step 1(e)) is inconsistent with PO’s litigation position

PO argues that neither Stahl nor So-456 teaches claim 1’s sequencing step because their methods sequence products that are generated downstream of (*i.e.*, after) the first cDNA products, which were reverse-transcribed from the sample

¹ The Petition and POPR refer to step 1(e) as the “sequencing step” and “identifying step,” respectively. *See, e.g.*, Pet., 29; POPR, 15.

² In contrast, the Petition is fully supported by the expert testimony of Dr. Spellman. *See* Pet., 53-55; EX1044, ¶¶187-192; *Roku, Inc. v. Universal Elecs., Inc.*, IPR2021-00758, Paper 7, at 29 (P.T.A.B. Sept. 27, 2021) (weighing Petitioner’s argument supported by expert testimony against Patent Owner’s bare attorney argument and finding that “[p]etitioner makes a sufficient showing”).

mRNAs. POPR, 15-20, 28-33. For example, PO argues that So-456 does not teach the sequencing step because “rather than sequence the first strand cDNA, or the ‘DNA product’ in the challenged claims, *So-456 teaches sequencing the second strand cDNA, a downstream product markedly different from the first strand cDNA.*” *Id.*, 32 (emphasis added). PO similarly argues that Stahl does not teach the sequencing step because Stahl’s method does not sequence “the cDNA reverse-transcribed from the sample mRNA...” *Id.*, 19; *see also id.*, 18. Thus, PO argues that claim 1’s sequencing step does *not encompass* sequencing DNA products that are generated downstream of the first cDNA products (which were reverse transcribed from the collected sample mRNAs in Stahl and So-456).

PO’s argument to this Board is inconsistent with its position in the concurrent district court litigation, where PO alleged that claim 1’s sequencing step *encompasses* sequencing DNA products that are generated downstream of the first cDNA products reverse transcribed from the collected sample mRNAs. EX1022, 22-24. In the litigation, PO alleged that 10x’s Visium Fresh-Frozen (FF) product infringes claim 1’s sequencing step because in Visium FF, “[l]ibraries are generated from the cDNA [reverse transcribed from sample mRNA] and sequenced and the Spatial Barcodes are used . . . for spatial gene expression mapping.” *Id.*, 23 (emphasis added). PO also identified Visium FF’s Steps 4 and 5 to allege infringement of the sequencing step. *Id.*, 22-24. However, Visium FF’s Steps 4 and

5 involve sequencing (in Step 5) a spatial gene expression library that was constructed (in Step 4) from the DNA products generated *downstream* of the first cDNA products, which were reverse transcribed from the collected sample mRNAs (Steps 1-3). *Id.*, 10-14, 18-21; EX1015, 17-18.

Thus, PO alleged in district court litigation that claim 1's sequencing step *encompasses* sequencing DNA products that are generated downstream of the first cDNA products (such as a sequencing library) to spatially detect the sample mRNAs—which is exactly what both Stahl and So-456 teach in their methods. EX1022, 22-24; Pet., 29-31, 65-67; *see also, e.g.*, EX1016, 78-80, FIGs. 1, 2, Suppl. Materials 4-7; EX1005, ¶¶[0002], [0088]-[0089], [00141], [00157]-[00158], [00302], [00307]-[00320], FIGs. 1A, 2, 24, 25. But now PO argues that Stahl's and So-456's methods of sequencing the DNA products downstream of the first cDNA products do *not* meet claim 1's sequencing step. PO's new position should be rejected. As the Petition demonstrated, both Stahl and So-456 teach the sequencing step under PO's litigation claim interpretation. *Id.*

II. The POPR's argument regarding claim 1's synthesis steps (steps 1(c) and 1(d)) is also inconsistent with PO's litigation position

PO argues that neither Stahl nor So-456 discloses claim 1's synthesis steps because both Stahl's and So-456's methods do not involve a synthesis reaction that incorporates a spatial barcode into the DNA product. POPR, 21-25, 33-38. PO admits that “the resulting products” from Stahl's (and So-456's) reverse

transcription reaction “comprise a spatial barcode,” but argues that the prior art methods “*do[] not incorporate* the spatial barcode,” which is already present in the capture probes. POPR, 22 (emphasis added), 34; *see also id.*, 23, 24 (“The spatial barcode is not incorporated through the reverse transcription reaction.”), 34 (“This reverse transcription reaction that Petitioner relies upon, however, does not incorporate a spatial address region.”).

PO’s argument to the Board is again inconsistent with its position in litigation. In district court, PO alleged that 10x’s Visium FF infringes claim 1’s synthesis steps by performing the same type of synthesis reaction as taught in Stahl and So-456—*i.e.*, using the capture probes (comprising spatial barcode sequences) as primers and captured sample mRNA as templates for reverse transcription, such that the resulting DNA products (*i.e.*, first cDNA products) comprise a spatial barcode. EX1022, 18-20, 22; Pet., 26-29, 61-64; *see also, e.g.*, EX1016, 78-79, FIG. 1, 2, S2, Suppl. Materials, 4-5; EX1005, ¶¶[00141], [00302], [00307]-[00308], [00314]-[00320], FIGs. 1A, 24, 25.

PO’s infringement allegations point to Visium FF’s two synthesis steps: Step 1 (reverse transcription reaction using the capture probe as a primer and the collected sample mRNA as a template to generate first cDNA products), and Step 2 (second-strand synthesis using the DNA product from Step 1 as a template). EX1022, 18-20, 22. While PO’s infringement allegations point to both of Visium

FF's synthesis steps, Visium FF's Step 2 (second-strand synthesis) cannot form the basis of PO's infringement allegations because Visium FF's Step 2 does not use the "collected oligonucleotides" (*i.e.*, captured sample mRNAs) as templates for the synthesis reaction, as required by claim 1. *Id.*; EX1015, 17; EX1043, 147:42-53 (requiring "a synthesis reaction that uses the plurality of oligonucleotides collected in step (a) [and step (b)] as templates"). Rather, the templates in Visium FF's Step 2 synthesis are the *DNA products* generated in Step 1 (not the captured sample mRNAs). EX1022, 18-20, 22; EX1015, 17.

Thus, PO's infringement allegations for the synthesis steps could only be based on Visium FF's Step 1, which uses the capture probe (comprising a spatial barcode) as a primer and the captured sample mRNA as a template, such that the first cDNA products from the synthesis reaction comprise a spatial barcode. *Id.* This process is the same type of synthesis reaction taught in Stahl and So-456. Pet., 26-29, 61-64; *see also, e.g.*, EX1016, 78-79, FIG. 1, 2; EX1005, ¶¶ FIGs. 1A, 24, 25. Accordingly, as the Petition demonstrated, both Stahl and So-456 teach claim 1's synthesis steps under PO's litigation claim interpretation. *Id.*

In conclusion, PO argued for a broad claim scope in the district court litigation and now a much narrower claim scope in its POPR. PO cannot have it both ways. The Board should reject PO's inconsistent arguments here, apply PO's litigation claim constructions as set forth in the Petition, and institute this IPR.

Respectfully submitted,

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PETITIONER'S PRE-INSTITUTION
REPLY** was served in its entirety on February 2, 2024, upon the following parties
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