

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DROPWORKS, INC.,
Petitioner,

v.

THE UNIVERSITY OF CHICAGO,
Patent Owner.

Case No. IPR2021-00100
Patent No. 8,304,193

PETITIONER'S PRE-INSTITUTION REPLY¹

¹ Authorization for this reply regarding §325(d) was given by email on
March 11, 2021.

Patent Owner invokes 35 U.S.C. §325(d), falsely arguing the prior challenge by 10X Genomics was substantially the same and merely relied on prior art “*identical* to the prior art relied upon in the instant Petition” POPR 24-25, 31 (emphasis added). Patent Owner is simply wrong.

I. PATENT OWNER MISCHARACTERIZES THE PRIOR RECORD AND THIS IPR

Unlike here, the prior proceedings lacked prior art teaching PCR amplification in a microscopic aqueous droplet having a water-oil interface. Pet. 71-75. In contrast, each of Holliger, Litborn, and Schneegaß disclose successful (i.e., actual reduction to practice) PCR amplification in microscopic w/o (water in oil) droplets.

The 10X challenge relied on Haff (IPR) and Kopp (reexamination). Neither reference describes PCR in microscopic aqueous volumes having an oil interface using the “traditional hydrocarbons” in Quake. PO falsely argued such oils were bioincompatible and would “destroy proteins,” rendering PCR impossible. Indeed, the Board found Haff deficient because (unlike each of Holliger, Litborn, and Schneegaß) Haff did not perform PCR in sub-microliter volumes and, as Patent Owner admits, Haff used air to segment its milliliter-sized samples. Pet. 8-9; POPR 23 (Haff “was not a droplet system...slugs of fluid are separated from one another by *air*” (emphasis added)). Kopp employed no different fluid phase at all, but only an aqueous blank between aqueous sample segments. Pet. 15 (citing EX1011,

1047).

Each of Holliger, Litborn, and Schneegaß is materially different and each proves incorrect Patent Owner's argument that 1) PCR had never been performed in microscopic w/o droplets; and 2) the oils Quake disclosed would have made PCR essentially impossible. Pet. 24, 56, 74-75. These new prior art references refute Patent Owner's continued attempts to argue PCR was impossible in microfluidic droplets formed in conventional oils, whereas the '193 patent was a "dream" realized (POPR 7). *Oticon Med. AB v. Cochlear Ltd*, IPR2019-00975, Paper 15, at 19 (precedential) (error not to consider prior art teaching what led to allowance).

The POPR argues mere citation to Quake here weighs "overwhelmingly" against institution. POPR 27. But such singular focus on one reference is incomplete under *Becton Dickinson*; it addresses neither the newly cited references nor the combination, which presents argument not previously considered. Moreover, Patent Owner ignores the fact there is no dispute Quake discloses generating w/o droplets in a microfluidic device as required by the challenged claims. The 10X challenge established prosecution error regarding Quake, and the Office then found no deficiencies in Quake for generating the plugs in a microfluidic system. Pet. 8-10. Patent Owner's singular fixation on Quake is misplaced.

II. PATENT OWNER MISCHARACTERIZES THE CONTENT OF THE PRIOR ART

Where the POPR does address Holliger, Litborn, and Schneegaß, it denies they address PCR amplification in microscopic w/o droplets despite express disclosure to the contrary. Based on such mischaracterizations (and individual attacks on references), the POPR asserts the art and arguments are substantially the same. POPR 29-31.

The POPR (31), for example, falsely claims “Litborn is not even a droplet reference” and “the same is true with respect to the Schneegaß reference.” Litborn expressly describes, and even illustrates graphically, droplet separation from the channel wall during hydrocarbon flow. EX1007, 452-53 & Fig. 7; *see also* EX1009, 109-10; Pet. 20-22. POPR arguments that Litborn and Schneegaß’s droplets are not droplets are at odds with the express content of the references themselves. Patent Owner attempts to pivot away from Litborn, pointing to a different Curcio reference (EX2003). POPR 19, 31. If considered, Curcio confirms that PCR amplification was successful in microfluidic droplets formed in decane or in fluorinated oil, further corroborating non-cumulative motivation and reasonable expectation discussion in the present petition. EX2003, Abstract, 4-5 & Figs. 2-3.

Patent Owner also mischaracterizes Holliger. Pet. 17, 31. The POPR points to Fig. 2, which actually depicts PCR droplet size remaining stable at ~15 microns even after PCR thermocycling. EX1006, 52:25-53:6. Nothing in Holliger supports

the speculative attorney argument that PCR might occur only in large droplets.

Patent Owner's argument also is not commensurate with the '193 patent. Holliger's 15-micron PCR droplets depicted in Fig. 2 each amount to a volume of about 2 picoliters, whereas the patent's preferred droplet size range extends from femtoliters up to "hundreds of nanoliters." Pet. 5-6, 30; EX1001, 11:24-53, 19:45-57, Figs. 3, 12, 27; EX1002, ¶¶38, 40; *see also* Pet. 18 (noting Quake's preferred droplet size of 0.1-100 picoliters). Holliger's 15-micron droplets are thus well-within the patent's range. Furthermore, Holliger does not teach that 15 microns was the only droplet diameter for PCR, and further teaches PCR could be performed in even smaller droplets. Pet. 23 (citing EX1006, 12:21-23). Holliger thus provides an additional counterexample that, like Litborn and Schneegaß, disproves Patent Owner's argument that bioincompatibility of conventional oils would preclude PCR in w/o droplets have sub-microliter volumes.

POPR (17, 31) argument that Holliger created a "mess" of droplets with "disparate size distributions" also ignores the proposed combination entirely, including non-cumulative argument regarding droplet formation benefiting from Quake's monodisperse microfluidic droplets with high throughput. Pet. 22-23, 26; EX1005, 27:27-32; *id.*, 82:25-27 (20-80 Hz).

Respectfully submitted,

Dated: March 12, 2021

/ Michael T. Rosato /

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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Petitioner's Pre-Institution Reply was served on March 12, 2021, on the Patent Owner at the following electronic correspondence addresses:

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