

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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DROPWORKS, INC.,  
Petitioner,

v.

THE UNIVERSITY OF CHICAGO, INC.,  
Patent Owner.

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

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**PATENT OWNER’S PRE-INSTITUTION SURREPLY**

***Mail Stop* “PATENT BOARD”**  
Patent Trial and Appeal Board  
U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

## PATENT OWNER'S EXHIBIT LIST

<u>Exhibit Number</u>	<u>Description</u>
2001	Whitesides, G., <i>The origins and the future of microfluidics</i> , Nature, Vol. 442, 368-373 (July 27, 2006)
2002	Teh, S.Y. et al., <i>Droplet microfluidics</i> , Lab Chip, 2008, 8, 198-220
2003	Curio, M., <i>Continuous Segmented-Flow Polymerase Chain Reaction for High-Throughput Miniaturized DNA Amplification</i> , Analytical Chemistry 2003, 75, 1-7, Bates-stamped DROPWORKS006407- DROPWORKS006413
2004	Request for <i>Ex Parte</i> Reexamination of U.S. Patent No. 8, 304,193 (Nov. 3, 2017)
2005	Ex Parte Reexamination Communication Transmittal Form (Sept. 28, 2018)
2006	Response to First Office Action in <i>Ex Parte</i> Reexamination of U.S. Patent No. 8,304,193 (June 12, 2018)
2007	Collins et al., <i>The Poisson distribution and beyond: methods for microfluid droplet production and single cell encapsulation</i> , Lap on a Chip (July 20, 2015)
2008	Seemann et al., <i>Droplet based microfluidics</i> Report On Progress Physics (December 22, 2011)
2009	Payne et al., <i>High-throughput screening by droplet microfluidics: perspective into key challenges and future prospects</i> , Lab on a Chip, Royal Society of Chemistry (May 28, 2020)
2010	Leng, et al., <i>Microfluidic crystallization</i> , Lab on a Chip, May 6, 2008, 24-34
2011	Zhu, et al., <i>Analytical detection technique for droplet microfluidics—A review</i> , Analytica Chimica Acta 787 (2013), 24-35
2012	Dropwork's Continuum Digital Flow PCR System, <a href="https://www.dropworks.com/introducing-continuum">https://www.dropworks.com/introducing-continuum</a>

Petitioner's Pre-Institution Reply repeats the same arguments it makes in the Petition and again fails to address the core reason why this IPR should not be instituted. Petitioner contends in its reply that Patent Owner "mischaracterizes" the content of the prior art. In fact, it was Petitioner that took liberties with vague disclosures in the Holliger, Litborn, and Schneegaß references to try and stretch the disclosure of these references far beyond what they actually teach. While Petitioner repeatedly asserts that these references were not relied upon in the many previous challenges against the '193 Patent, this is simply because they are poor references that are far from the claims of the '193 Patent.

As an initial matter, Petitioner's reply makes little mention of the Quake reference, which is Petitioner's *primary reference* and is relied upon for virtually all claim elements. Petitioner does not deny that it is relying upon Quake in the exact same way and for the exact same purpose as the previous unsuccessful challengers to the '193 Patent. As Patent Owner explained, however, the skilled artisan would not have been motivated to perform any kind of autocatalytic reaction (let alone PCR) based on Quake. Ex. 2006 at 3, Ex. 1026 at 35, POPR at 33-36. Quake teaches away from performing PCR in droplets, explaining that "the significant risk of cross contamination from sample to sample can outweigh the benefits of detecting small quantities of a target viral nucleic acid." Ex. 1005 at 3:3-5. Petitioner's reply does not address this.

Strangely, Petitioner criticizes Patent Owner for allegedly having a “singular fixation” on Quake. Petitioner’s attempt to downplay the importance of its *own* primary reference in this manner is a tacit acknowledgment of the weakness of its position. Regardless, Patent Owner’s preliminary response was not fixated on Quake, but rather accurately addressed head-on the content of *all* of Petitioner’s references, including Holliger, Litborn, and Schneegaß.

As to Holliger, Petitioner focuses on the fact that it is different from the Kopp and Haff references previously relied upon in unsuccessful challenges to the ’193 Patent. If anything, however, Holliger is even further afield from Quake than Kopp or Haff. Kopp and Haff at least involved something that resembled a microfluidic system, but Holliger is nothing of the sort. In Holliger, random forces from a paddle or whisk are used to generate a bulk emulsion having 113 million water vesicles of unknown size distribution. *See* POPR at 16-17, *see also* Ex. 1006 at Fig. 2.

Although Petitioner argues that Patent Owner has mischaracterized Holliger, none of the foregoing is disputed. It is also undisputed that Holliger provides no indication as to what fraction or type of vesicles actually yielded a product. Holliger’s alleged ability to capture some PCR product from 113 million water containers in a bulk emulsion says nothing about the conditions for doing PCR across a much smaller number of droplets of tightly controlled size in microfluidic devices, provides no motivation to perform such an experiment, and does not

establish a reasonable expectation of being able to successfully do so.

Petitioner contends that Patent Owner's arguments about Holliger's failure to disclose the sizes and types of vesicles that actually yielded a PCR product is speculation. This, however, fails to acknowledge that it is the Petitioner's burden to establish that Holliger's droplets would have been compatible with Quake, not the Patent Owner's burden to prove the negative. As Patent Owner pointed out, it simply would not have been possible to identify which of Holliger's droplets contained successful PCR products, showing that a POSA would not have been motivated to look to combine Holliger and Quake.

In an attempt to discredit Patent Owner's arguments, Petitioner suggests that some of Holliger's droplets are within the range of sizes described by the '193 Patent. Reply at 4. This misses the point. The '193 Patent teaches using microfluidics to create uniform, monodisperse droplets that allows for precise control of PCR. Holliger's method, on the other hand, generates a wide distribution of vesicle sizes, a fact that Petitioner does not deny. Even if some vesicles are within the range of sizes described by the '193 Patent, that does not show that a POSA would have combined Holliger with Quake.

As to Litborn and Schneegaß, Petitioner's reply includes nothing to establish that they are any different from segmented flow devices like Haff and Kopp. Petitioner points to Figure 7 of Litborn as supposedly showing droplet PCR. But

Figure 7 is just a pencil sketch of a droplet. Ex. 1007 at 452. Petitioner relies upon Litborn's disclosure of "preliminary experiments with a flow based PCR reaction." Ex. 1007 at 453, *see also* Petition at 60, 67. Yet, it is undisputed that Litborn includes *nothing* regarding these experiments. A little investigation reveals that these experiments were later published in the Curcio reference, a point Petitioner does not deny. While Petitioner asserts Curcio involved droplets, Petitioner does not justify this. As Patent Owner explained, Curcio cannot possibly be a droplet system because the oil and water are never connected simultaneously to the system. POPR at 38-39. That Curcio does not use droplets is confirmed by its title, which refers not to droplets, but "segmented-flow." *See* Ex. 2003. While Petitioner asserts that Patent Owner has mischaracterized the art, Petitioner's misplaced reliance on Litborn shows that it is Petitioner that has misunderstood the art.

Finally, as to Schneegaß, it is clear that Schneegaß only describes performing PCR in a segmented flow device. Schneegaß describes various chip designs for flowing reagents through a channel, much like Kopp and Haff. Ex. 1009 at 108, Fig. 5. As Patent Owner explained, where PCR is described, the reagents are in contact with the glass in the channel well, and are thus not droplet devices, where the reagents are entirely surrounded by an immiscible oil. *See* Ex. 1009 at 108, Fig. 5. While Schneegaß suggests using oil may help prevent contamination, Schneegaß's paper describes only forming droplets and not performing PCR in them. *Id.* at 109.

Respectfully submitted,

Dated: March 26, 2021

/s/ Derek C. Walter

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## **CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 5,279 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Dated: March 26, 2021

/s/ *Derek C. Walter*

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## CERTIFICATE OF SERVICE

I hereby certify that on March 26, 2021 a copy of the foregoing **PATENT OWNER'S PRE-INSTITUTION SURREPLY** was served by filing this document through the Patent Office's electronic systems as well as delivering a copy via electronic mail upon the following counsel of record:

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