

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Control No.: 90/014,043

Filed: February 9, 2011

Patent No.: 8,304,193

Patent Issued: November 6, 2012

For: METHOD FOR CONDUCTING AN  
AUTOCATALYTIC REACTION IN  
PLUGS IN A MICROFLUIDIC SYSTEM

Confirmation No.: 7357

Examiner: Elizabeth L. McKane

Art Unit: 3991

Submitted Via Electronic Filing On:

June 12, 2018

Mail Stop Petition  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**RESPONSE TO FIRST OFFICE ACTION IN *EX PARTE* REEXAMINATION OF U.S.  
PATENT NO. 8,304,193**

## I. INTRODUCTION

The University of Chicago submits this paper in response to the Office Action in Ex Parte Reexamination dated April 13, 2018. Claims 1-14 of U.S. Patent No. 8,304,193 (“the ’193 patent”) stand rejected under 35 USC § 103(a) based on Quake in view of Kopp and/or Shaw-Stewart.

This reexamination is closely related to two other reexaminations involving patents in the same family as the ’193 patent in which the claims also stand rejected based on the combination of Quake with Kopp and/or Shaw-Stewart. The Requester in all three reexaminations is 10X Genomics, Inc., which is accused of infringing in district court litigation that has been pending since February 2015.

All of the patents at issue pertain to pioneering work by Professor Rustem Ismagilov and colleagues at the University of Chicago<sup>1</sup> for conducting chemical reactions in microfluidic droplets. Based largely on this work, Professor Ismagilov became one of the 100 most-cited chemists in the world during the 2000-2010 timeframe. For confirmation of just how important and innovative Ismagilov’s work is, one need look no further than the 2007 publication of Requester’s expert from failed IPR petitions that it previously pressed against Ismagilov’s patents. As Requester’s expert, Dr. Wilhelm Huck, acknowledged, microfluidic droplets were a “unique platform” for carrying out chemical reactions that offered numerous benefits and that was of “great interest”:

Microdroplets formed within microfluidic devices present a unique platform for the miniaturization of chemical and biochemical reactions.<sup>1</sup> The principal benefits lie in the ability to create nanolitre to femtolitre-sized individual reactors in which the contents can be accurately controlled.<sup>2,3</sup> This is of great interest for areas of research where a multitude of reaction conditions with minimum amounts of reactants need to be tested, e.g., in high-throughput screening of chemical reactions, protein crystallization, and enzyme kinetics.<sup>4,5</sup>

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<sup>1</sup> Professor Ismagilov is now at the California Institute of Technology.

Ex. 2023 at 984. Of the five citations in this paragraph, four are to the work of Ismagilov and colleagues. Researchers have repeatedly praised their work as “major,” “elegant,” and “seminal.” *See* Exs. 2030, 2020, 2013.

Nevertheless, in all three reexaminations, the Examiners have preliminarily stated that Ismagilov’s patents are obvious because a person of ordinary skill in the art would have combined Quake with Kopp and/or Shaw-Stewart to perform PCR reactions in microfluidic droplets. Patent Owner submits, however, that the skilled artisan simply would not have achieved PCR in droplets using Quake as a starting point.

Indeed, Quake was the primary prior art reference during prosecution of most of Ismagilov’s patents, including two of the three patents at issue in the instant reexaminations. One examiner—after reviewing Quake carefully during four separate prosecution proceedings—became “convinced” that Ismagilov and colleagues—not Quake—had “pioneered” PCR reactions in droplets:

As a result of these discussions the examiner allows the claims of the instant application, because the Applicants convinced the examiner that they pioneered performing PCR reactions in flowing droplets in the high-competitive field of microfluidics related to biochemical applications.

Ex. 2020 at 430. Likewise, as noted above, after Requester was sued for infringement, it attempted to invalidate Ismagilov’s patents through IPRs. Despite this Office’s prior consideration of Quake, Requester again attempted to rely upon Quake as the primary reference

in a reconstruction of art that supposedly led to PCR in droplets. All of the Requester's IPRs, however, failed emphatically.<sup>2</sup>

These prior determinations were not due to error or oversight, but instead due to the fact that Quake is nowhere close to the '193 patent. Far from suggesting PCR in droplets, Quake teaches that the droplet technique is an *alternative* to PCR to sort cells or particles (e.g., viral particles). Quake is thus wholly oblivious to the parameters for achieving PCR in droplets. In fact, Quake hardly mentions *any kind* of reaction in droplets. To the extent Quake makes brief mention of reactions, it proposes a speculative technique based on droplet merger that is nothing like the claimed invention of the '193 patent. The skilled artisan would have thus had to make major modifications to Quake to achieve PCR in droplets in the manner of the '193 patent. As documented below, the skilled artisan would not have been motivated to make these changes, and would not have had a reasonable expectation of successfully doing so.

The Examiner's rejection should be withdrawn.

## II. THE STATE OF THE ART AND THE LEVEL OF ORDINARY SKILL

The question of whether the '193 patent is obvious can only be evaluated with a proper understanding of the relevant technological context in the 2002 time frame, including the state of the art and the competencies of the skilled artisan. It is critical to understand that the state of the art of microfluidic droplet technology at the relevant timeframe was completely undeveloped because this reveals just how advanced the invention was for its time. As documented below, the

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<sup>2</sup> In most cases, the PTAB concluded that the Requester had not even made a threshold showing sufficient to warrant institution of an IPR. *See, e.g.*, Ex. 2028 at 18 ("We are not persuaded that the combination of Haff's reactants and conditions for a PCR method with Quake's aqueous plugs in a microfluidic system likely would have been obvious based on the evidence of record."); Ex. 2027 at 16 (We "determine that Petitioner has not explained why a person of ordinary skill in the art would have had a reasonable expectation of success combining Haff's capillary tube PCR system with Quake's microfluidic system to amplify a substrate in *droplets*." (emphasis in original)).

nascent state of the art is confirmed not just by contemporaneous technical literature, but also by the testimony of Requester's own expert from its failed IPR proceedings. It is further confirmed by the testimony of Patent Owner's expert, Professor Samuel Sia of Columbia University.<sup>3</sup> *See generally* Sia Decl. ¶¶ 30-39.

As late as 2006, prominent microfluidics researcher George Whitesides of Harvard University characterized the entire field of microfluidics as a field in "infancy." *See, e.g.*, Ex. 2003 at 372 ("So, what next for microfluidics? It is both a science and a technology. It offers great—perhaps even revolutionary—new capabilities for the future. It is also in its infancy, and a great deal of work needs to be done before it can be claimed to be more than an active field of academic research."). Likewise, he characterized the field as being in "early adolescence," lacking a "broad range of different types of component and subsystem, and their integration into complete, functional systems." *Id.* at 369. As yet another example, he characterized the field as being "still at an early stage of development." *Id.* at Abstract.

As a matter of pure logic, because microfluidics was in its infancy in 2006, it was even more nascent in 2002. *See* Sia Decl. ¶ 33. And, the particular subfield of microfluidics that is the subject of the '193 patent (microfluidic droplets) was almost entirely undeveloped. As Requester's expert acknowledged, "I think in 2002, it was a – the droplets in microfluidics field was relatively new." Ex. 2017 at 52:19-20. Requester's expert testified that in 2002 he was aware of only *one* literature reference related to droplets in microfluidics devices, a 2001 publication by Quake and Thorsen in the journal *Physical Review Letters*:

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<sup>3</sup> Professor's Sia declaration ("Sia Decl.") is attached hereto as Exhibit 2001.

**Q.** Well, all this line of questioning is about the field of microfluidic devices you've defined in Paragraph 13. So going back to that field, other than the physical review letters paper that you identified, is there any other resources that you can think of in the 2002 time frame that would have given people in the field of microfluidic devices awareness of the use of droplets?

**A.** At the top of my head, I cannot think of other examples in scientific journals where people were using microdroplets in microfluidic devices.

Ex. 2005 at 243:2-12. This brief four-page publication has subject matter that overlaps with the Quake reference relied upon by Requester, but is short on detail. It is merely an initial report regarding the formation of droplets.

As Requester's expert confirmed, in 2002, researchers were focused not on droplets, but on continuous flow and segmented flow of liquids and reagents:

**Q.** Okay. And so as of 2002, would you agree that that [segmented flow] type of work was what was conventional in the microfluidics field?

**A.** I don't know whether you would call that "conventional," but I think the segmented flows were well established.

**Q.** Okay. Those are the tried and true techniques as of 2002?

**A.** Sorry. The –

**Q.** The segmented flow techniques were the tried and true techniques as of 2002?

**A.** I think as of 2002, there was much more literature available in the segmented flows than on flows where the droplets are completely surrounded.

*Id.* at 229:6-19; *see also id.* at 240:10-14 ("So I think in 2002 there was probably a significant community working on segmented flows in the field of microfluidics, but not a large fraction of people working on the droplets that are completely surrounded by the carrier fluids").

In both segmented and continuous flow systems, there are no droplets. *See* Sia Decl. ¶¶ 34, 61-64. Continuous flow systems involve continuous streams of liquid. In segmented flow, there are simply segments of fluid that contact channel walls and that are separated from one

another by a segmenting fluid, which can be a gas such as air. The Kopp reference is an example of such a system. *Id.*

While segmented and continuous flow techniques were known in 2002, basic techniques related to microfluidic droplets were not widely known. *Id.* ¶¶ 36-37. For instance, Requester's IPR expert did not even begin researching microfluidic droplets until sometime in 2003. *See* Ex. 2017 at 36:9-21. In 2004, he, along with other researchers, applied for funding for a project related to microfluidic droplets. As part of their proposal, their initial research objective was to first establish basic techniques in microfluidic droplets, including (1) techniques for generating microdroplets within microfluidic systems so that the droplets can be loaded with e.g. enzymes, substrates, inhibitors, DNA, etc. in a defined way, (2) sorting and splitting droplets, (3) assaying reactions in droplets, and (4) integrating these features into microfluidic devices. *See* Ex. 2031 at 3, § J. Because these techniques were not yet established, Dr. Huck and team needed to research and develop them *ab initio*, because without doing so, they would be unable to convince the funding agency that they could carry out further research:

I think at that stage the field was new and one – as we were starting to work in that direction, we had to allow time to build up the expertise for generating microdroplets within microfluidics systems so that they could be loaded with enzymes, substrates, inhibitors, and DNA, and that we could then sort and split those droplets and that we could then assay reactions in those droplets because otherwise, we could not convince the research councils that we could carry out the second part of the proposals.

Ex. 2005 at 254:13-22.

Prior to Ismagilov, little was known about other important aspects of microfluidic droplets as well. For instance, researchers in the field had little information regarding the selection of appropriate carrier fluids for microfluidic droplets. *See* Sia Decl. ¶¶ 37, 50-51, 82. Requester's expert confirmed at deposition that the only information would have come from Quake's four-page publication in *Physical Review Letters*:

**Q.** Right. But in terms of what carrier fluids could be used for a droplet system as of May 2002, the only thing you were aware of – your knowledge based on that was what was in the Quake PhysRevLet letter?

**A.** Yes. As I explained, I'm not a person who has knowledge of all the pertinent art. And so I was aware of what was in the PhysRevLet paper.

**Q.** And that's it?

**A.** And that's it.

Ex. 2017 at 84:15-23.

Likewise, those of skill in the art would have had little information regarding the appropriate surfactants for use in a droplet system, in particular appropriate fluorinated surfactants. As Requester's expert explained in a 2010 review article, such surfactants were not even widely available until the 2006 timeframe. Ex. 2009 at 5852 (“[U]ntil recently fluorinated surfactant options for microdroplet experiments were limited.”); *see also* Ex. 2017 at 168:23-169:13.

As of 2002, the field of droplets in microfluidic devices was so new that the skilled artisan would not have even been familiar with the relevant technical challenges. The testimony of Requester's IPR expert is illustrative:

**Q.** What was the technical challenges [sic] to a droplet system in a microfluidic device – as of 2002?

**A.** I don't know the technical challenges that one would need to overcome to make droplets – microdroplets in a microfluidic device in 2002.

Ex. 2017 at 185:13-22 (objection omitted).

In sum, researchers interested in droplets in microfluidic devices in 2002 would have been working from a blank slate, not just with regard to solutions to problems, but also as to the very identity of the relevant problems. Although the skilled artisan may have been aware of the concept of droplets in microfluidic devices, the skilled artisan would not have known how to generate droplets with reagents in defined ways, would not have known how to split and sort

droplets, would not have known how to mix reagents in droplets, would not have known how to assay reactions in droplets, and would not have known how to integrate these concepts into a single microfluidic device. Likewise, little information was available regarding the appropriate oils and surfactants for use in a microfluidic droplet device, and the skilled artisan would have had to research this. In researching this issue, the skilled artisan likely would have uncovered numerous new and unpredictable problems related to how reagents and materials interact with the materials used to construct the device and the oils and surfactants used.

With such limited knowledge available to the skilled artisan at the relevant timeframe, a finding of obviousness should be supported by unusually compelling evidence. The Examiner has not come close to providing such evidence.

### **III. RESPONSE TO REJECTION BASED ON THE COMBINATION OF QUAKE WITH KOPP AND/OR SHAW-STEWART**

“The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness.” M.P.E.P. § 2142; *see also Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1378 (Fed. Cir. 2015) (“Dome’s appeal arises from an ex parte reexamination of the ‘042 patent. Ordinarily, the Patent Office in such a proceeding must establish by a preponderance of the evidence that the reexamined claims are not patentable.”); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1255 (Fed. Cir. 2013) (“The Board erroneously placed the burden on Rambus to prove that its claims were not obvious. In reexamination proceedings, ‘a preponderance of the evidence must show nonpatentability before the PTO may reject the claims of a patent application.’”).

As documented below, the Examiner has failed to meet its burden of showing that the claims of the ’193 patent are not patentable based on Quake in view of Kopp and/or Shaw-Stewart.

### **A. The Cited Prior Art Fails To Teach Key Claim Elements**

The claims of the '193 patent cannot be regarded as obvious unless all claim elements are disclosed or suggested in the art in some way. *See, e.g., Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1062 (Fed. Cir. 2016) (denying JMOL of invalidity, explaining that “Apple also presented substantial evidence on which a reasonable jury could find that the combination of Robinson and Xrgomics failed to disclose every claimed element.”); *St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) (“We see no error in the district court’s legal conclusion of nonobviousness. Neither Takayasu nor Smiley discloses a balloon configured to operate as a positioning device to prevent a plug from entering a blood vessel as claimed in the Fowler patents. Takayasu discloses no balloon at all, and Smiley discloses a balloon that is used to control the bleeding of a gunshot wound or an abdominal aneurism.”).

Quake, Kopp, and Shaw-Stewart fail to disclose or suggest several key claim elements such that the '193 patent cannot be deemed obvious in view of this art. Consideration of the claim elements missing from the cited art underscores just how different the prior art is from the claimed invention and how unsuitable it is for use in an obviousness combination.

#### **1. The Cited Prior Art Fails To Disclose Conditions Suitable For Conducting PCR In Microfluidic Droplets**

The prior art—taken alone or in combination—fails to disclose or suggest perhaps the most significant element of the claimed invention: “providing conditions suitable for the autocatalytic reaction in the at least one plug such that the at least one substrate molecule is amplified.” Here, the Examiner’s rejection is based on the “reaction” being PCR, such that the Examiner must show that the prior art discloses or suggests conditions suitable for conducting PCR in droplets.

The Examiner in the reexamination of U.S. Patent No. 8,304,193, however, has acknowledged that Quake does not specify conditions for conducting PCR in microfluidic droplets. *See, e.g.*, Office Action at 4 (“nor does Quake specify the conditions are suitable for an autocatalytic reaction”). Indeed, the Examiner does not contend in any of the reexaminations that Quake teaches conditions suitable for PCR in droplets.

Therefore, the Examiner cites to Kopp (which discloses standard thermal cycling for PCR) and/or Shaw-Stewart (which discloses “heating means”) to find a disclosure of this claim element. Ostensibly, the Examiner is of the view that conducting PCR in microfluidic droplets requires one to do nothing more than package PCR reagents in a droplet and then apply a traditional PCR thermal cycling protocol to the droplet as a whole. This view, however, is incorrect, and the Examiner’s rejection is based on a mistaken premise. *See generally* Sia Decl. ¶¶ 75-97.

Microfluidic droplets present a unique chemical environment that must be accounted for if one wants to use them as reaction vessels. *See id.* ¶¶ 23-24, 76-78. This is particularly true for enzymatic reactions, such as PCR. Most important, one cannot ignore the surface chemistry and biocompatibility issues that result from the tiny volumes of microfluidic droplets and their large surface to volume ratios.<sup>4</sup> *Id.* As the ’193 patent explains, “[c]ontrol of surface chemistry is particularly important in microfluidic devices because the surface-to-volume ratio increases as the dimensions of the systems are reduced.” Ex. 1001 at 35:59-61.

While the reaction mixture of Kopp is in contact with an inert glass surface, the volume of a tiny microfluidic droplet is surrounded by a chemical carrier fluid that carries the droplets

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<sup>4</sup> Specifically, because the surface area of a sphere is  $4\pi r^2$  and the volume of a sphere is  $\frac{4}{3}\pi r^3$ , the surface to volume ratio of an approximately spherical droplet goes as  $1/r$  and thus increases rapidly as the radius of the droplet decreases.

down the microfluidic channel. Because the volume of the droplet is so small, the contents of the droplet are in regular contact with the surface of the droplet. *See* Sia Decl. ¶¶ 23-24, 76-78. Thus, to carry out biological chemical reactions in microfluidic droplets, one must develop a droplet/carrier-fluid interface inert to the adsorptions of proteins and cells yet that still allows droplets to flow smoothly through microfluidic channels. *Id.* ¶ 78.

For instance, one publication recognized the “great importance” of selecting the right “oil/surfactant system” to avoid protein adsorption:

Given the large surface to volume ratio of microdroplets, surface interactions at the oil/water interface are of great importance in selecting the oil/surfactant system so as to interfere minimally with the cells and biologically active molecules contained in the droplet. Certain combinations of fluorinated oils and (ionic) fluorosurfactants have been demonstrated to result in nonspecific protein adsorption at the interface.[54] Protein adsorption at the droplet surface may have detrimental effects where functional proteins are involved, such as in enzyme assays or screening.

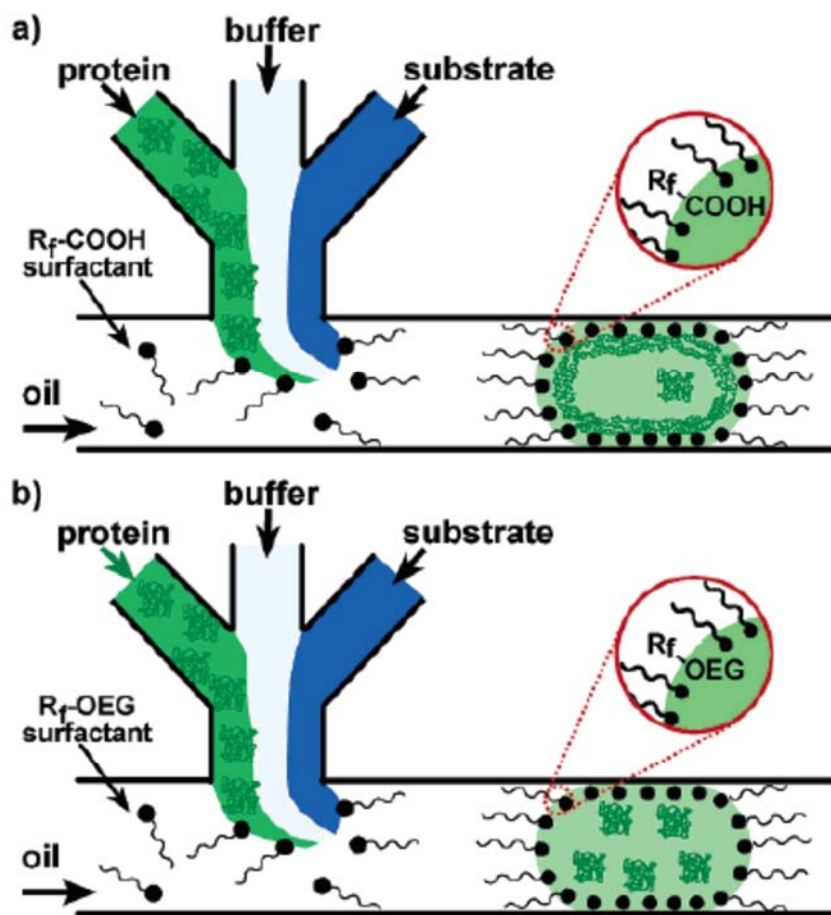
Ex. 2012 at 12181. Notably, citation 54 in the block quote above is a landmark paper by Ismagilov and team describing use of the very oil/surfactant system described in the Chicago patents for providing conditions suitable for enzymatic reactions in droplets.

Citing this very same paper, the Requester’s expert from the IPR proceedings acknowledged that one cannot simply assume that a biological reaction may be carried out by applying traditional reaction conditions to a droplet as a whole. Rather, as he explained, “biocompatibility” of the reagents vis-à-vis the droplet surface must be dealt with:

With each biological experiment biocompatibility of the reagents has to be tested anew. For examples, oligoethylene glycol-terminated surfactants prevent non-specific adsorption of protein to the water–oil interface.[71] This is an important consideration as the large surface-to volume ratio can strongly affect the outcome of enzymatic reactions in droplets.

Ex. 2009 at 5852 (citing L. S. Roach, H. Song, R. F. Ismagilov, *Anal. Chem.* 2005, 77, 785).

The following figure from the Ismagilov publication cited by Requester's IPR expert depicts how failure to create a properly biocompatible droplet surface can lead to destruction of the proteins in a droplet:



**Figure 1.** Controlling surface chemistry in plug-based microfluidic devices with surfactants at the aqueous-fluorous interface. (a, b) Schematic of surfactant molecules at the interface of an aqueous plug of protein in a microfluidic channel. (a) R<sub>f</sub>-COOH surfactant provided a noninert interface prone to protein adsorption. (b) R<sub>f</sub>-OEG surfactant provided an inert, biocompatible interface.

Ex. 2011, Fig. 1. As the top image shows, use of an incorrect oil/surfactant system leads to destruction of proteins and thus does not provide suitable conditions for PCR in droplets. Yet, as shown in the bottom image, use of a proper oil/surfactant system prevents proteins from sticking to the droplet surface and allows one to use droplets for enzymatic reactions.

The oil/surfactant system described in the paper above is precisely the system described in the Chicago patents. *See* Sia Decl. ¶¶ 103-08. As the Chicago patents explain, “[c]ontrol of surface chemistry is particularly important in microfluidic devices because the surface-to-volume ratio increases as the dimensions of the systems are reduced.” Ex. 1001 at 35:59-61. To this end, the Chicago patents disclose a system that integrates both fluorinated oils and fluorinated surfactants having a hydrophilic oligoethylene glycol head group for the specific purpose of providing conditions for conducting biological reactions in droplets. *See* Sia Decl. ¶¶ 79-82. That is, the fluorinated chemistry Ismagilov developed provides “biocompatible” reaction conditions.

First, with regard to the use of fluorinated oil, the Chicago patents expressly explain that such oils are attractive due to their biocompatibility properties:

Using perfluorocarbons as carrier-fluids in surface studies are attractive because they are in some cases more biocompatible than hydrocarbons or silicones. This is exemplified by the use of emulsified perfluorocarbons as blood substitutes in humans during surgeries. Controlling and modifying surface chemistry to which the reagents are exposed can be achieved simply by introducing appropriate surfactants into the fluorinated PFD phase.

Ex. 1001 at 36:11-19. Another literature reference makes the following additional points regarding the benefits of fluorinated oils:

For drops to be truly functional microvessels, however, there must not be any cross-contamination between the drops. For this, it is attractive to use a fluorocarbon oil as the continuous phase as these oils are both hydrophobic and lipophobic, hence they have low solubility for the biological reagents of the aqueous phase and are well suited for inhibiting molecular diffusion between drops. In addition, as compared to hydrocarbon oils, fluorocarbon oils result in less swelling of polydimethylsiloxane (PDMS), a commonly used material for fabricating microfluidic channels. Finally, fluorocarbon oils have good solubility for gases, which is necessary for the viability of encapsulated cells.

Ex. 2010 at 1632. In other words, the fluorinated oil not only serves to provide an interface that is compatible with biological molecules, but also serves to trap the reagents inside the droplet so that the droplet can actually be an effective chamber for a reaction. *See* Sia. Decl. ¶¶ 80-81.

As to the fluorinated surfactant, the Chicago patents further describe fluorinated surfactants that create an inert surface that prevents destruction of proteins and that can be integrated with the fluorinated oil:

Fluorosurfactants terminated with OEG-groups have been shown to demonstrate biocompatibility in blood substitutes and other biomedical applications. Preferably, oil-soluble fluorosurfactants terminated with oligoethylene groups are used to create interfaces in the microfluidic devices in certain applications. Surfactants with well-defined composition may be synthesized. This is preferably followed by the characterization of the formation of aqueous plugs in the presence of those surfactants. Their inertness towards nonspecific protein adsorption will also be characterized. FIG. 24 shows examples of fluorinated surfactants that form monolayers that are: resistant to protein adsorption; positively charged; and negatively charged. For OEG-terminated surfactants, high values of  $n$  ( $\geq 16$ ) are preferred for making these surfactants oil-soluble and preventing them from entering the aqueous phase. In FIG. 24, compounds that have between about 3 to 6 EG units attached to a thiol are sufficient to prevent the adsorption of proteins to a monolayer of thiols on gold, and are thus preferred for inertness. In addition, surfactants that have been shown to be biocompatible in fluorocarbon blood substitutes may also be used as additives to fluorinated carrier fluids.

Ex. 1001 at 36:38-59. This type of integrated oil/surfactant system for achieving suitable conditions for biochemical reactions proposed by Ismagilov was new and important and was not disclosed in the prior art. *See* Sia Decl. ¶¶ 81-82.

Against this backdrop, the PTAB previously made clear during 10X's failed IPR proceedings that conditions necessary for conducting PCR in a droplet must take into account the unique chemical environment of a microfluidic droplet. Specifically, in construing the claim term "conditions suitable for a polymerase-chain reaction in at least one plug of the plurality of plugs such that the target DNA or RNA is amplified," the PTAB explained as follows:

At this stage of the proceeding, we determine that Patent Owner's interpretation is more consistent with the plain and ordinary meaning of the claim term, which requires more than a single stimulus to induce a reaction. We are persuaded by Patent Owner's argument that the specification sets forth certain conditions that must be addressed when conducting PCR in a microfluidic droplet, including unwanted adsorption of proteins on the surface of the droplet. Accordingly, we construe the claim term as requiring conditions that allow the substrate molecule to be amplified in a microfluidic system.

Ex. 2027 at 9 (citations omitted).<sup>5</sup>

When it comes to PCR in droplets, the Requester does not disagree with this construction. Indeed, the Requester specifically noted the Board's conclusion that the "specification sets forth certain conditions that must be addressed when conducting PCR in a microfluidic droplet, including unwanted adsorption of proteins on the surface of the droplet." *See* Request for *Ex Parte* Reexamination in 90/014,045 at 50.

This interpretation naturally follows from the specification, which repeatedly emphasizes the importance of surface chemistry for conducting reactions in droplets and identifies numerous examples taking into account the surface chemistry:

- "Third, achieving control over the chemistry of internal surfaces of devices can be very **important** at small scales. Thus, being able to control surface chemistry in small devices for example is highly desirable. In accordance with the devices and methods according to the invention, the surface chemistry to which solutions are exposed is preferably controlled through a careful selection of surfactants that are preferably designed to assemble at the interface between the plugs and the immiscible fluid that surrounds them." *See* Ex. 1001 at 12:9-17.
- "Control of surface chemistry is **particularly important** in microfluidic devices because the surface-to-volume ratio increases as the dimensions of the systems are reduced. In particular, surfaces that are generally inert to the adsorption of proteins and cells are invaluable in microfluidics." *Id.* at 35:59-63.

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<sup>5</sup> District Court Judge Richard Andrews of the District of Delaware construed the claims similarly, making clear that the "conditions" must be a "set of physical and chemical conditions that allow the [autocatalytic reaction/reaction/polymerase-chain reaction] to occur." *See* Ex. 1055 at 1.

- “The manipulation and control of the surface chemistry can be used for screening, assays, crystallizations, and other applications where surface chemistry is important.” *Id.* at 57:18-21.
- “Controlling and modifying surface chemistry to which the reagents are exposed can be achieved simply by introducing appropriate surfactants into the fluorinated PFD phase.” *Id.* at 36:16-19.
- “To address the sensitivity of blood coagulation to surfaces (the cascade is normally initiated on the surface), microscopic beads containing immobilized tissue factor (the cascade initiator) on the surface may be added to one of the streams and transported inside the plugs. Also, surfactants may be used to control surface chemistry.” *Id.* at 47:13-18.
- “Their inertness towards nonspecific protein adsorption will also be characterized. FIG. 24 shows examples of fluorinated surfactants that form monolayers that are: resistant to protein adsorption; positively charged; and negatively charged.” *Id.* at 36:46-50.

Consistent with the specification, the literature regarding droplet microfluidics has repeatedly acknowledged Ismagilov’s work, in the process making clear that the surface chemistry issues associated with droplets are “crucial,” “major,” of “great importance,” and an “important consideration” for conducting reactions in droplets. *See* Sia Decl. ¶¶ 84-89. While the unique droplet/carrier-fluid surface chemistry issues associated with microfluidic droplets are dealt with at length in the ’193 patent, none of Quake, Kopp, or Shaw Stewart address such issues and none come close to teaching conditions suitable for conducting PCR in droplets. *See* Sia Decl. ¶¶ 90-93.

#### **a. Quake Does Not Teach Conditions Suitable For PCR In Droplets**

As noted above, the Examiner acknowledges that Quake does not disclose conditions for PCR in a droplet at all. Indeed, Quake discloses no working examples of any kind of reaction in droplets, disclosing at most a speculative technique based on droplet merger that is nothing like the ’193 patent. *See generally* Sia Decl. ¶¶ 44-49. Quake thus cannot possibly disclose

conditions suitable for the reaction in a droplet. A careful review of the disclosure in Quake confirms this to be the case.

As Patent Owner's expert explains, although Quake is about droplets, it makes no mention of the issues associated with the interface between the droplet and the carrier fluid that must be addressed to carry out PCR in droplets. *See* Sia Decl. ¶¶ 42-43, 91-92. In fact, Quake is focused on a completely different interface, specifically, the interface between the carrier fluid and the channel wall. Indeed, Quake repeatedly mentions that the walls should be coated with some substance to avoid particle adhesion, but he never mentions the key issues that are connected to the interface between the carrier fluid and the droplet fluid. *See, e.g.*, Ex. 1034 at 35:18-29; Sia Decl. ¶¶ 91-92. Quake certainly does not teach any appropriate oil/surfactant system that provides conditions suitable for a PCR reaction.

Rather than teaching fluorinated oils as a carrier fluid, Quake uses traditional hydrocarbons, such as decane, tetradecane, hexadecane, and mineral oil, which are not remotely biocompatible and will destroy proteins. *See* Ex. 1034 at 6:8-10, 8:16-18; Sia Decl. ¶ 93. Quake only mentions fluorinated compounds twice, suggesting that they can be a minor additive to the carrier fluid, but not for creating biocompatibility. Rather, they are for the purpose of coating channel walls. *See id.* Ex. 1034 at 35:18-29; Sia Decl. ¶¶ 91-92. Thus, Quake again focuses on the wrong interface. Regardless, the presence of a fluorinated oil as a secondary additive to decane, tetradecane, hexadecane, or mineral oil carrier fluid, as Quake suggests, will not help achieve suitable biocompatible conditions for PCR in a droplet. Sia Decl. ¶ 92. Certainly, a fluorinated oil does not have an appropriate head group for this purpose. *Id.*

Further, even if one assumed Quake were seeking to use surfactants at the correct interface for creating conditions suitable for PCR in droplets, Quake does not teach the right

surfactants for this purpose. *See* Sia Decl. ¶ 93. Despite providing a laundry list of surfactants, *see* Ex. 1034 at 28:7-23, 35:18-21, all of them are wrong. Other than fluorinated oils (which do not have the proper head group), none of the surfactants proposed by Quake are fluorinated, and thus none are appropriate for use with a biocompatible fluorinated carrier fluid.

As Patent Owner's expert explains, Quake includes no disclosure of any appropriate carrier fluid for use with any of the disclosed surfactants that would create suitable conditions for PCR in droplets. *See* Sia Decl. ¶ 93. With the possible exception of the polyoxyethylenated polyoxypropylene glycol surfactants, all of the surfactants listed by Quake include head groups that do not avoid protein adsorption and that would be harmful to proteins, including surfactants with highly-polar alcohol, carboxylic acid, thiol, and amino groups. *Id.* As to the polyoxyethylenated polyoxypropylene glycol surfactants, they are not fluorinated, and, moreover, Quake specifies them at such a high-level of generality it is unclear specifically what he is proposing and whether he is proposing surfactants that actually have head groups sufficient to help avoid protein adsorption. *Id.* In short, there is nothing in Quake that would point one of skill in the art to an appropriate oil/surfactant system to create conditions suitable for PCR in droplets.

Notably, at the time the Quake application was filed, PCR was a well-known biological reaction that was critical to researchers worldwide, and had been so for many years prior. Yet, Quake does not disclose PCR in droplets, and Quake's research group ***never*** published any work regarding any kind of successful chemical reactions in droplets, let alone PCR. If carrying out sophisticated chemical reactions, such as PCR, in droplets were truly as straightforward as the Examiner suggests, then it is difficult to understand why Quake never did any such work.

Of course, the explanation is that conditions for carrying out such reactions are not obvious. Indeed, while Quake never published any successful work regarding reactions in droplets, Quake's graduate student, Todd Thorsen, did document his unsuccessful efforts to integrate a biochemical enzyme assay with microfluidic droplets. *See* Sia Decl. ¶ 38. As Thorsen explained in his thesis, the "crossflow assay was unreliable," Ex. 2006 at 100, and resulted in "*hundreds*" of failed efforts "ultimately discarded in an attempt to discover the perfect operating conditions." *Id.* at 101-102. As Thorsen stated, "[w]orking on the development of a microfluidic crossflow assay emphasized the difficult dynamic integration process between biochemical and micromechanical systems." *Id.* at 108. Thorsen's final prognostication was as follows:

While problems such as non-specific cell adhesion and substrate autohydrolysis plagued the assays, the results are not intended to discourage future research in this area. Improvements in areas such as surface chemistry technology and reagent stability will promote the development of cell-based, sensitive biochemical assays in this system.

*Id.* at 108.

Quake never figured out how to conduct any kind of reaction in droplets, let alone PCR.

**b. Shaw-Stewart Does Not Teach Conditions Suitable For PCR In Droplets**

Shaw-Stewart, like Quake, also discloses an approach based on droplet merger, and includes no working examples or data. *See, e.g.*, Ex. 1040 at 1:15-19 ("moving the inert immiscible liquid and discrete volumes through the conduit system in such a manner that predetermined discrete volumes coalesce with each other thereby combining the reagents"); Sia Decl. ¶¶ 55-59. As such, although Shaw-Stewart possibly suggests a heating element that allows channels to be heated, it does not teach conditions suitable for conducting a PCR reaction in droplets, and is oblivious to the relevant surface chemistry issues. In fact, PCR was not even

invented until after the Shaw-Stewart application was filed. *See id.* ¶ 60. Shaw-Stewart thus could not possibly contemplate or disclose conditions suitable for PCR in droplets.

**c. Kopp Does Not Teach Conditions Suitable For PCR In Droplets**

Finally, as to Kopp, although it teaches PCR in glass channels, it is not even a microfluidic droplet reference and thus cannot possibly teach the conditions necessary for conducting PCR reactions in droplets. *See* Sia Decl. ¶¶ 62-64. Indeed, Kopp does not even use a carrier fluid that is immiscible with a reagent fluid. *Id.*

Because none of the prior art references disclose or suggest reaction conditions suitable for carrying out PCR *in droplets*, the Examiner has not stated a *prima facie* case of obviousness and the rejection should be withdrawn.

**2. The Cited Prior Art Fails To Teach A Continuously Flowing Aqueous Fluid Containing Both A Biological Molecule And A Reagent**

The claims of the '193 patent all require “continuously flowing an aqueous fluid containing at least one biological molecule and at least one reagent for conducting the reaction between the biological molecule and the at least one reagent through a first channel of the at least two channels.” None of the cited prior art suggests this claim element.

The Examiner acknowledges that Quake does not teach this claim element. *See* Office action in 90/014,045 at 3 (“While Quake does not teach that the aqueous fluid includes both a biological molecule and a reagent for reaction....”). The only piece of prior art that the Examiner suggests might disclose this claim element is Kopp. *See id.* at 5 (“With respect to claim 1, the PCR mixture as taught by Kopp would include both the biological molecule and reagent.”).

Kopp, however, does not disclose this claim element because the biological molecule and reagent in Kopp are not “continuously flowing.” *See* Sia Decl. ¶¶ 62-64. Rather, in Kopp,

discrete 10  $\mu$ l slugs of PCR mixture are injected one-by-one into the channels of the microfluidic device where they contact the channel walls and travel down the channel for collection. *See* Ex. 1027 at 1047 (“For each amplification, 10  $\mu$ l of PCR mixture was injected and collected at the outlet of the chip for analysis.”). This is nothing like the ’193 patent, where the reagents flow continuously into a stream of immiscible carrier fluid (such as a fluorinated oil) and droplets are formed by the interaction of the reagent fluid with carrier fluid. *See* Sia Decl. ¶ 64. Thus, the Examiner cites no prior art teaching this claim element.<sup>6</sup>

### **3. The Prior Art Fails To Teach Fluorinated Oils As Carrier Fluids**

Claim 6 of the ’193 patent requires the use of an “oil” that “is fluorinated oil.” This “oil” is the same thing as the “carrier fluid” referred to in claim 7, a point that Requester agrees with. *See, e.g.,* Ex. 1050 at 17 (“However, a POSA would have understood that the ‘carrier fluid’ of claim 7 is ‘the oil’ of claim 1.”). As independent claim 1 makes clear, the “oil”/“carrier fluid” is the substance that surrounds the droplets and carries the droplet down the channel. *See* Ex. 1001, claim 1 (explaining that the plug is “substantially surrounded by an oil flowing through the channel.”). This is also the substance that is used to “partition” the “plug fluid.” *Id.* (“partitioning the aqueous fluid with the flowing oil at the junction of the at least two channels”). Consistent with this, the specification makes clear that “plugs” are formed through the interaction of the plug-fluid with the “carrier fluid.” *See, e.g., id.* at 9:27-40. Thus, as used in the claims, the “carrier fluid”/“oil” must be distinguished from mere additives to the carrier fluid that are included for the purpose of, for instance, coating channel walls, but are not the fluids that actually partition the droplets, surround the droplets, and carry them down the channel. The

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<sup>6</sup> To the extent the Examiner suggests that this claim element is an obvious combination of Quake and Kopp, the reasoning discussed below establishes that one of skill in the art would not have been motivated to combine Quake with Kopp to achieve the claimed invention, nor would the skilled artisan have had a reasonable expectation that this combination would succeed. *See infra* Parts III.B and III.C.

specification is consistent with this throughout. *See, e.g., id.* at 17:50-18:13, 19:7-26, 21:25-39, 22:27-44, 29:35-47.

The use of a “fluorinated oil” carrier fluid is not taught in any of the prior art references. The only thing the examiner points to as possibly teaching this claim element is pg. 35, ll. 18-29 of the Quake reference.

The full passage from Quake cited by the Examiner is as follows:

The fluids used in the invention may contain additives, such as agents which reduce surface tensions (surfactants). Exemplary surfactants include Tween, Span, fluorinated oils, and other agents that are soluble in oil relative to water. Surfactants may aid in controlling or optimizing droplet size, flow and uniformity, for example by reducing the shear force needed to extrude or inject droplets into an intersecting channel. This may affect droplet volume and periodicity, or the rate or frequency at which droplets break off into an intersecting channel.

Channels of the invention may be formed from silicon elastomer (e.g. RTV), urethane compositions, or from silicon-urethane composites such as those available from Polymer Technology Group (Berkeley, CA), e.g. PurSil™ and CarboSil™. The channels may also be coated with additives or agents, such as surfactants, TEFLON, or fluorinated oils such as octadecafluorooctane (98%, Aldrich) or fluorononane

Ex. 1034 at 35:18-29. Nothing in this passage is a disclosure of using a fluorinated oil as a carrier fluid. *See* Sia Decl. ¶ 50. A plain reading of this passage shows that it at most discloses using a fluorinated compound as an “additive” in the fluid to coat the channel walls. Such a substance would neither partition nor surround the droplets, as recited in the claims. *See id.*

There should be no dispute that Quake does not disclose a fluorinated oil as a carrier fluid. Indeed, the Requester’s expert from the IPR proceeding repeatedly acknowledged that Quake simply does not disclose fluorinated oil as carrier fluid:

- Q.** Do you have any explanation why Quake did not disclose a fluorinated oil as a carrier?
- A.** Well, first of all, Ramsey says that perfluorocarbons are suitable fluid especially when compatibility is required.

- Q.** Okay. And just remember this. This isn't a debate where you argue your side. It's a question-and-answer format. So I was asking you about Quake, and then you answered something about Ramsey, which actually only makes my question more compelling or curiosity driving.
- A.** Yeah. Yeah.
- Q.** Which didn't Quake disclose a fluorinated oil for a carrier fluid?
- A.** I don't know.
- Q.** I mean you can't come up with any technological reason? I'm not asking you to psycho analyze it.
- A.** I don't know why Quake didn't come up with that.

Ex. 2017 at 77:23-78:17; *see also id.* at 75:11-13 (“**Q.** Quake does not disclose the use of a fluorinated oil for carrier fluid; correct? **A.** That is correct.”); *id.* at 165:19-166:6 (“**Q.** But I just want to just be sure – clear for the record, because I think it's important, can you explain any reason why Professor Quake would not have proposed fluorinated oil as one possible alternative for carrier fluid based on all the work that you've done in this case? **A.** No. I think you mentioned the perfluorinated oils as an example of a surfactant, but he didn't mention it as a carrier fluid.”); *id.* at 80:5-82:8 (“**Q.** We all agree – you've been point blank under oath – that Quake doesn't disclose use of fluorinated oil. **A.** That's right.”).

Because there is no disclosure in the prior art of the use of a fluorinated oil as a carrier fluid for a droplet device, the rejection should be withdrawn.

**B. The Person Of Ordinary Skill In The Art Would Not Have Been Motivated To Combine Quake With Kopp And/Or Shaw Stewart**

Obviousness requires a “showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.” *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011); *see also Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380

(Fed. Cir. 2015) (explaining that the factfinder “must further consider” “whether a person of ordinary skill in the art would be motivated to combine those references”).

Even if one assumes the prior art suggests all the claim elements, the Examiner has failed to meet its burden of establishing that the person of ordinary skill in the art would have been motivated to combine Quake with Kopp and/or Shaw Stewart to perform PCR in microfluidic droplets.

**1. Quake’s Citation To Kopp Does Not Provide The Requisite Motivation To Combine**

The Examiner first suggests that Quake’s citation to Kopp provides a motivation to combine Quake with Kopp to perform PCR in droplets. *See* Office Action in 90/014,045 at 3-4 (“Quake points directly to Kopp...for a teaching of an appropriate PCR system for integration.”). If Quake’s citation to Kopp, however, was truly some sort of express teaching that one should perform PCR in microfluidic droplets, then why didn’t Quake himself ever perform or disclose any examples of PCR in droplets at any point in time?

In fact, the portion of Quake pointed to by the Examiner is far from an express suggestion to carry out PCR in droplets. *See* Sia Decl. ¶ 47. The full passage cited by the Examiner is as follows: “Microfabrication permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR (13), moving cells using optical tweezer/cell trapping (14-16), transformation of cells by electroporation (17),  $\mu$ TAS (18), and DNA hybridization (5).” Office Action at 3; *see also* Ex. 1034 at 23:26-29. This sentence does nothing more than point out that PCR—and a bunch of other techniques—are possibilities for “microfabrication.”

Indeed, when Requester’s expert from the IPR proceedings was asked about this passage, he acknowledged that it was just a review of work by others regarding integration of a range of other technologies with flow cytometry:

**Q.** Let me ask you this: In Paragraph 80, this is a review by Quake of others' work showing that microfabrication by these others has combined flow cytometry on a single, separate chip with DNA hybridization, PCR, moving cells using optical tweezer cell trappings; right?

**A.** That's what it says.

Ex. 2017 at 183:9-15. The Examiner's view that Quake's reference to Kopp—among a string cite of seven different publications—is an express instruction to perform PCR in droplets reads far too much into vague and ambiguous language and thus can only stem from the improper use of hindsight.

The inappropriateness of the Examiner's reading of Quake becomes clear when one considers the remainder of Quake. The Background of the Invention begins with a lengthy description of detecting viruses and cells. *See* Ex. 1034 at 2:11-4:30. Quake describes two basic approaches that had been used in the prior art. One prior art approach was PCR. Quake explains, however, that PCR had the disadvantage of leading to false positives given its extreme sensitivity:

The advantage of PCR for viral diagnostics is its high sensitivity; PCR can detect very low numbers of viruses in a small clinical specimen. However, this sensitivity of detection can also cause significant problems in routine viral diagnostics. ***The significant risk of cross contamination from sample to sample can outweigh the benefits of detecting small quantities of a target viral nucleic acid. Cross contamination can also result in false positives, making interpretation of epidemiological data impossible.***

Ex. 1034 at 2:32-3:6. Other than the passing reference to PCR relied upon by the Examiner, there is no further mention of PCR in the entire Quake reference.

The second approach for detecting viruses and cells suggested by Quake in the Background of the Invention is particle sorting, using devices such as FACS and flow cytometry. *See id.* at 3:7-8 ("Flow sorting devices have been used to analyze and separate larger biological materials, such as biological cells."). Quake devotes nearly two full pages to discussing the details of problems associated with these devices. *See id.* at 3:7-4:30.

Then, immediately thereafter, in the very first sentence of the Summary of the Invention, Quake states that he is offering an improved version of FACS and flow cytometry for *sorting* that avoids the particular problems he identified:

The invention addresses the above-discussed and other problems in the art and provides new devices and methods *for sorting* viruses and other particles by flow cytometry. The invention provides microfabricated devices having channels that form the boundary for a fluid instead of using a sheath flow employed by conventional FACS.

*Id.* at 5:1-5. There is no mention of PCR. Rather, throughout the specification, Quake states repeatedly that it provides a technique for sorting particles that is an improved version of FACS or flow cytometry. *See* Ex. 1034 at Abstract (“A microfluidic device for analyzing and/or sorting biological materials....”); *id.* at 5:1-3 (“The invention addresses the above-discussed and other problems in the art and provides new devices and methods for sorting viruses and other particles by flow cytometry.”) *id.* at 34:14-15 (“According to the invention, molecules (such as DNA, protein, enzyme or substrate) or particles (i.e., cells, including virions) are sorted dynamically....”). “Sorting” (or some variation thereof) is mentioned 274 times in Quake.

As the foregoing proves, Quake is not directed to performing PCR at all, let alone PCR in droplets. Quake is focused on providing an alternative to PCR based on *sorting*, not a better way of doing PCR. *See* Sia Decl. ¶ 46. Indeed, even in Quake’s brief discussion of carrying out reactions using droplet merger, he never once suggests PCR as a possible reaction. At most, he suggests simple unimolecular enzymatic reactions. *See id.* Ex. 1034 at 85:9-86:22; Sia Decl. ¶ 46. Nowhere does Quake explain why it would make sense to do PCR in droplets, or why this would offer any sort of improvement over prior art PCR techniques.

“It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.”

*Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986).

Patent Owner respectfully submits that by relying on Quake's citation to Kopp without considering the full disclosure of Quake, the Examiner has failed to heed this guidance.

**2. Minimizing Cross Contamination And Increasing Throughput  
Cannot Provide A Motivation To Combine**

For the '193 patent, the only motivation to combine provided by the Examiner is Quake's passing reference to PCR. In the co-pending reexaminations, however, the Examiner further states that it "would have been obvious to utilize the continuous-flow microfluidic device of Quake to perform the PCR of Kopp with the introduction of the PCR mixture into the carrier fluid via the inlet channel of Quake to achieve encapsulated droplets which minimize cross-contamination and would allow for desired high throughput amplification of multiple samples flowing through simultaneously." *See, e.g.*, Office Action in 90/014,045 at 5. For completeness, Patent Owner addresses this rationale in connection with this response as well.

To the extent the Examiner is suggesting that the person of ordinary skill in the art would have been motivated to combine Quake with Kopp to perform PCR in a way that minimizes "cross contamination" and/or achieves "high throughput," such a motivation makes little sense.

Indeed, Kopp purports to already teach a PCR technique that minimizes contamination. *See* Ex. 1027 at 1047 ("We suggest that cross-contamination in a continuous-flow format may be much less of a problem than in a stationary-tube PCR format. Thus a flow-through PCR chip can be reused for extended periods without major cleaning."). Likewise, Kopp already claims to provide a PCR technique that offers high-throughput and allows for analysis of multiple samples. *See id.* ("Because multiple samples plugs can travel at the same speed through the same chip, the potential throughput of a single device can be greatly increased.").

Given that Kopp already teaches a high-throughput PCR technique that avoids contamination, it makes little sense to suggest that one would add the droplet technique of Quake to achieve such goals. Although a motivation to combine may stem from a desire to solve a known problem in the art, where the prior art already purports to provide a solution to the known problem the motivation to combine vanishes. *See, e.g., St. Jude*, 729 F.3d at 1381 (no motivation to combine where prior art references already taught two solutions to “known problem in the art”).

### **3. Quake And Kopp Are Incompatible References That Would Require Extensive Modification To Be Combined**

As the Examiner acknowledges, to the extent Quake includes any disclosure of techniques for carrying out chemical reactions, it discloses techniques based on somehow merging different droplets with different reagents by some undisclosed mechanism at some unknown time to initiate a chemical reaction by some unidentified mechanism. *See* Office Action in 90/014,045 at 3 (“The system is also structured such that two droplets may be mixed and such that reactions may occur within the mixed droplet.”). Quake discloses no working examples of this technique, and Quake’s research group never subsequently published any work on this approach.

Regardless, the ’193 patent—unlike Quake—does not use droplet merger to carry out chemical reactions. Instead, the ’193 patent generates droplets *de novo* with all reagents for carrying out a reaction. Thus, achieving the claimed invention based on Quake would require a re-design of Quake’s approach from one based on making multiple droplets and merging them to an approach based on generating droplets with multiple reagents *de novo*. The Examiner does not offer any justification for why the person of ordinary skill in the art would change Quake’s system in this manner. In this light, Patent Owner respectfully submits that the Examiner has

impermissibly used the invention as a roadmap to reconstruct the prior art such that the rejection is fundamentally flawed. *See InTouch Techs., Inc. v. VGO Commcns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (“Dr. Yanco’s testimony was vague and did not articulate reasons why a person of ordinary skill in the art at the time of the invention would combine these references. It appears that Dr. Yanco relied on the ‘357 patent itself as her roadmap for putting what she referred to as pieces of a ‘jigsaw puzzle’ together.”) (internal citation omitted).

Further, the fact that achieving the claimed invention based on Quake would require changing Quake’s principle of operation confirms just how different Quake is from the claimed invention and strongly weighs against a finding of obviousness. *See, e.g., In re Ratti*, 270 F.2d 810, 813 (C.C.P.A. 1959) (reversing obviousness rejection where the “suggested combination of references would require a substantial reconstruction and redesign of the elements shown” in the prior art “as well as a change in the basic principles under which the [prior art] construction was designed to operate”); *see also* M.P.E.P. § 2143 (“If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.”).

Yet further confirmation of the awkwardness of the Examiner’s proposed combination of art emerges when one considers how poorly Quake fits with the Kopp reference. *See* Sia Decl. ¶¶ 62-74. The system of Kopp is not a droplet system in which a carrier fluid is used, but is instead a system in which a discrete reagent volume is injected directly into a microfluidic channel and is in contact with the channels. This presents flow conditions that are “fundamentally different” from those present in a true droplet system (such as Quake), a point confirmed by another of Requester’s IPR experts:

- A. I’ve explained that, in droplet systems, the droplets do not – no. They’ve – they’ve come – the droplets have been – been formed, and they don’t necessarily contact the walls of the container.

Whereas, in segmented flows, the segmented flows are contained within the full width of the container.

**Q.** And from a flow perspective, do you consider that to be fundamentally different?

**A.** I do.

Ex. 2032 at 94:13-95:2; *see also* Sia Decl. ¶¶ 73-74. As set forth in further detail in the accompanying affidavit of Patent Owner's expert, Dr. Samuel Sia of Columbia University, the person of ordinary skill in the art simply would not have drawn inspiration from a system like Kopp when seeking to modify a true droplet system like Quake's and would have faced several problems. *See id.* ¶¶ 65-74.

In this regard, the Examiner does not explain precisely how one of skill in the art would combine Quake with Kopp, or what kind of system would supposedly result from this combination. An obviousness theory that omits such an explanation is "fraught with hindsight bias." *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (affirming finding of nonobviousness where the "expert failed to explain how specific references could be combined, which combination(s) of elements in specific references would yield a predictable result, or how any specific combination would operate or read on the asserted claims.").

To the extent the Examiner is suggesting using Quake's droplet merger system with Kopp, which does not use merger, the Examiner never explains why droplet merger would be a benefit for PCR or why it would make sense to separate the different reagents into different droplets. More likely, the Examiner is suggesting putting droplets in a microfluidic system configured like Kopp. Yet, the Examiner never addresses whether the person of ordinary skill in the art would have thought such a combination was technically feasible or reasonable such that he or she would have been motivated to make such a combination.

For instance, would the thermal cycling system of Kopp be adequate for PCR in microfluidic droplets that are insulated by a carrier fluid? The Examiner does not address this. What changes to Quake, if any, would be needed to maintain droplet stability under the thermal cycling conditions required for PCR? The Examiner also does not address this. What changes would be needed to Kopp to take into account the speed at which droplets are carried in the channels of the microfluidic system? The Examiner does not address this either. In fact, as explained by Patent Owner's expert, given the speed at which droplets travel, applying the system of Kopp to Quake would require a total channel length at least 11.5 meters in length, and likely much longer. *See* Sia Decl. ¶¶ 66-68. Was this feasible for the kinds of materials and technology used in the relevant timeframe to make microfluidic droplet systems? Even if it were, why would the person of ordinary skill in the art be motivated to create such a complex system?<sup>7</sup>

The multiplicity of issues that would need to be addressed to combine Quake with Kopp are a consequence of the fact that droplet systems are very different from systems of the type disclosed in Kopp. Patent Owner respectfully submits that the person of skill in the art in the relevant timeframe would not have been motivated to make such a combination.

**C. The Person Of Ordinary Skill In The Art Would Not Have Had A Reasonable Expectation Of Success**

The Federal Circuit has “held that where a party argues a skilled artisan would have been motivated to combine references, it must show the artisan would have had a reasonable

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<sup>7</sup> Notably, the Requester's own expert from its failed IPR proceedings documented these sorts of issues in a 2010 review article, stating that because of the speed at which droplets travel they were “not suitable” for processes that occur on extended time frames. *See* Ex. 2009 at 5854 (“Typical residence times for droplets in microfluidic devices are in the range of seconds to minutes, which means that they are not suitable for studying processes which occur on a timescale of minutes to hours, which would be typical for many chemical reactions as well as biological experiments involving the incubation of cells or the in vitro expression of proteins.”).

expectation of success from doing so.” *Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.*, 876 F.3d 1350, 1360–61 (Fed. Cir. 2017) (internal citation and quotations omitted). The Examiner bears the burden of showing this reasonable expectation of success. *See* M.P.E.P. § 2142. The Examiner has not met its burden.

Indeed, the Office Action does not even mention reasonable expectation of success. As such, the Examiner has failed to provide the “articulated reasoning with some rational underpinning” that is required “to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (quoted with approval in *KSR*, 550 U.S. at 418). For this reason alone, the rejections are legally deficient and should be withdrawn.

In fact, there cannot possibly be a reasonable expectation of successfully combining Quake with Kopp and/or Shaw Stewart to perform PCR in droplets because, as documented above, none of the prior art discloses the conditions suitable for conducting enzymatic reactions in droplets. *See infra* Part I.A.1. The Requester’s expert from the IPR proceedings made clear that one cannot just assume that conducting reactions in droplets is as simple as packaging reagents in droplets:

With each biological experiment biocompatibility of the reagents has to be tested anew. For examples, oligoethylene glycol-terminated surfactants prevent non-specific adsorption of protein to the water–oil interface.[71] This is an important consideration as the large surface-to volume ratio can strongly affect the outcome of enzymatic reactions in droplets.

Ex. 2009 at 5852 (citing L. S. Roach, H. Song, R. F. Ismagilov, *Anal. Chem.* 2005, 77, 785). As documented above, none of the prior art addresses such issues and none of the prior art provides the guidance that would permit a person of ordinary skill in the art to have a reasonable expectation of being able to perform PCR in droplets.

Further, as documented above and in the accompanying declaration of Patent Owner’s expert, the person of ordinary skill in the art would have recognized that droplet systems and

segmented flow systems such as Kopp are very different. *See, e.g.*, Sia Decl. ¶¶ 62-74. As a result, he or she would have had to address several issues to combine a droplet system with a segmented flow system like the one disclosed in Kopp. *See supra* pp. 29-32. The Examiner has not established that the person of ordinary skill in the art would have had a reasonable expectation of being able to successfully do so.

**D. Secondary Considerations Demonstrate That The Chicago Patents Are Not Obvious**

As documented in the accompanying declaration of Patent Owner's expert, scientists have repeatedly praised the inventive work of the Chicago patents teaching how to carry out reactions in droplets. *See* Sia Decl. ¶¶ 98-108. This praise comes in the form of the citation record for literature describing experiments that embody the claimed inventions of the Chicago patents. *See id.* ¶¶ 98-101. Likewise, it comes in the form of express praise for the specific techniques that Ismagilov and team developed for carrying out reactions in droplets. For example, Leng, J., et al., "Microfluidic crystallization," *Lab on a Chip* 9:24-34 (2009), characterized Dr. Ismagilov and his group's research in this area as "major work":

Ismagilov et al. did major work concerning droplet micro-fluidics and concerning the chemistry of the surfactants and oils used to perform the above experiments.<sup>61</sup> Indeed, in order to mimic perfect microbatch conditions, they identified fluorinated oils that were nearly impermeable to water, and synthesized oligoethylene glycol-capped perfluorinated surfactants that prevented protein adsorption at the interface of the droplets. To handle membrane proteins, they also used perfluoroamines that provided high surface tension.

Ex. 2013 at 29 (reference 61 is to Ismagilov's publication disclosing a surfactant/oil system that provides conditions suitable for PCR in droplets). Other researchers have characterized Ismagilov's work as "seminal" and "elegant." *See* Exs. 2030, 2020; *see also* Sia Decl. ¶¶ 76, 80, 84, 86, 87-89.

If Ismagilov's work were truly obvious, it would not have been praised so extensively. This praise stands as a compelling objective indicator of the nonobviousness of the Chicago patents.

#### **IV. SUMMARY OF EXAMINER INTERVIEW**

On June 5, 2018, representatives of the Patent Owner (Derek Walter, Naishadh Desai, and Matthew York) participated in an interview with Examiners Jastrzab, McKane, and Witz regarding the reexamination of the Chicago patents. Patent Owner thanks the Examiners for their time in meeting with the Patent Owner.

During the interview, Patent Owner summarized the distinction between microfluidic droplet technology and prior art microfluidic systems, such as those based on segmented flow. Patent Owner further explained why none of the cited prior art references disclosed conditions suitable for conducting enzymatic reactions, such as PCR, in droplets. In particular, the content of section I.A.1 of the instant response was discussed. Patent Owner further explained why the skilled artisan would not have been motivated to combine the cited prior art to perform PCR in microfluidic droplets.

#### **V. CONCLUSION**

For the foregoing reasons, the University of Chicago requests that the Examiner withdraw its rejection under 35 U.S.C. § 103 based on the combination of Quake with Kopp and/or Shaw-Stewart.

Respectfully submitted,

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