

Filed: August 17, 2015

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.
Petitioner,

v.

THE UNIVERSITY OF CHICAGO
Patent Owner

Case IPR2015-01163
Patent 8,304,193

**THE UNIVERSITY OF CHICAGO'S PRELIMINARY RESPONSE TO
PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,304,193
PURSUANT TO 37 CFR § 42.107**

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I. INTRODUCTION

Patent Owner The University of Chicago submits this Preliminary Response to Petition For *Inter Partes* Review of U.S. Patent No. 8,304,193 (“the Petition”). For the reasons stated below, the Board should not institute review.

U.S. Patent No. 8,304,193 (“the ’193 patent”) is one of a suite of patents awarded to Rustem Ismagilov and co-workers at the University of Chicago that describe complete systems for carrying out reactions in microfluidic droplets.¹ According to the Petitioner’s expert, “the microfluidics field was mature” and relevant systems “had been constructed since the 1950’s.” Ex. 2006 [Ex. 1002 in ’573 IPR] ¶ 46. Yet, despite 60 years of research, the Petition alleges only obviousness and fails to identify a single reference that teaches chemical reactions in microfluidic droplets. Petitioner effectively concedes that in 60 years, despite all the publications and research efforts in this field, no one had ever discovered the inventions protected by the claims of the ’193 patent.

The use of microfluidic droplets as chemical microreactors was at most an aspiration until Ismagilov and co-workers made this goal a reality. When Ismagilov and co-workers published their innovations, researchers in the field quickly described them as “elegant” and “seminal,” and have cited them over

¹ Professor Ismagilov is now at the California Institute of Technology.

4,000 times. The Petitioner's expert himself has recognized the importance of this work, in 2007 describing the use of droplets for carrying out reactions as a "unique platform" 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.¹ The principal benefits lie in the ability to create nanolitre to femtoliter-sized individual reactors in which the contents can be accurately controlled.^{2,3} 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.^{4,5}

Ex. 2007 [Fidalgo, et al. Lab Chip 2007] at 984. Of the five citations in this paragraph, four are to the work of Ismagilov and colleagues.

The significance of the inventions only becomes clearer when one analyzes the art relied upon in the Petition. Of the two main references, only Quake is even in the microfluidics field. During prosecution of each of the Ismagilov patents, the Examiner considered Quake, either in the form of a patent filing or a journal publication. After reviewing Quake carefully, one Examiner became "convinced" that Ismagilov and colleagues 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. 1020 at 430.² The Examiner was correct. Quake and his graduate student attempted to carry out a model enzymatic reaction in droplets and failed, lamenting the “problematic” integration of their droplet generating device with “biochemical systems.” Ex. 2008 [Thorsen Dissertation 2003] at 101-02. Unsurprisingly, the Quake reference includes no more than a speculative suggestion of reactions in droplets, and does not even mention PCR in droplets.

To attempt to fill this gap, the Petition awkwardly relies upon the Haff reference, which discloses PCR in capillary tubes, not droplets. The Petitioner’s expert acknowledges that Haff operates on a size-scale orders of magnitude greater than expected in a microfluidic system. And Haff is expressly directed to *increasing* the volume of a PCR reaction, the exact opposite of what one hopes to achieve by using droplets “for the miniaturization of chemical and biochemical reactions.” Ex. 2007 [Fidalgo, et al. Lab Chip 2007] at 984.

Starting from these dissonant references, the Petition is necessarily unable to provide the articulated reasoning with rational underpinning that is required to

² A second examiner reviewed Quake independently during prosecution of U.S. Patent No. 8,889,083, which is at issue in IPR2015-01157, and similarly concluded that the Ismagilov team’s inventions were patentable over Quake.

support a conclusion of obviousness. Rather, the Petition strains to combine Quake and Haff by misapprehending the art. Further, neither the Petition nor Petitioner's expert provides any explanation as to how one of skill in the art would actually combine Quake with Haff. Similarly, the Petition provides only conclusory assertions as to reasonable expectation of success that epitomizes the problem of using hindsight to over-read the prior art. The technological gulf between Quake and Haff is a major red-flag that the legal standard to institute this proceeding is not satisfied.

The Petition does not establish a reasonable likelihood that it will prevail as to at least one claim of the '193 patent. That patent is an important invention being infringed by the Petitioner. The Board should not allow this IPR to proceed further; such proceedings would surely be used to attempt to delay the infringement litigation between the parties.

II. BACKGROUND

A. The Relationship Among Petitioner's Five IPR Requests

In early May 2015, Petitioner requested *inter partes* review ("IPR") of five related patents awarded to Rustem Ismagilov and co-workers. These patents are infringed by Petitioner and are the subject of litigation in the District of Delaware. *See RainDance Techs. et al. v. 10X Genomics, Inc.*, No. 15-152-RGA (D. Del. filed Feb. 12, 2015). Collectively, these patents will be referred to as the "Ismagilov

Patents.” The Ismagilov Patents have substantially overlapping specifications and describe complete systems for carrying out a variety of chemical reactions in microfluidic droplets.

Patent Owner’s preliminary responses fully address Petitioner’s proposed grounds of invalidity. For the convenience of the Board, the following table summarizes the grounds of invalidity addressed in each response:

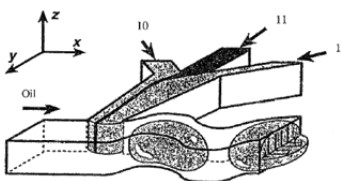
Patent	IPR No.	<u>§ 103:</u> Haff + Quake	<u>§ 103:</u> Quake + Ramsey	<u>§ 102:</u> Quake	<u>§ 103:</u> Haff + Quake + Ramsey	<u>§ 103:</u> Quake + Ramsey + Green
8,822,148	2015-1156	X				
8,304,193	2015-1163	X			X	
8,329,407	2015-1158	X			X	
8,273,573	2015-1162	X		X	X	
8,889,083	2015-1157		X			X

For three of the five Ismagilov Patents, Petitioner relies primarily on obviousness based on the combination of the Quake and Haff references, presenting nearly identical arguments. Accordingly, Patent Owner’s responses are very similar. In the 1162 IPR, Petitioner again relies on Quake and Haff, but also makes a flawed anticipation argument based on Quake. In the 1157 IPR, the Petitioner relies on the combination of Quake, Ramsey, and Green and presents different arguments relative to the other four Ismagilov patents. Patent Owner’s preliminary response in that IPR is thus substantially different than its other responses.

B. The '193 Patent

Each of the Ismagilov Patents describes complete systems for carrying out a variety of chemical reactions in droplets in microfluidic systems. Microfluidic systems involve the transport and manipulation of fluids on a tiny scale, using channels that typically have micrometer dimension. *See, e.g., '193 patent at 1:20-22.* While microfluidic systems were commonly based on laminar, uninterrupted flow of liquids through microfluidic channels, the inventions of the Ismagilov Patents are based on the use of microfluidic droplets, called “plugs” in the Ismagilov Patents.

The Ismagilov Patents include a detailed description of how such plugs are formed. *See '193 patent at 17:24-21:67.* Plugs are formed by introducing a laminar stream of a plug fluid into the flow of a carrier fluid immiscible with the plug fluid. For instance, the plug fluid may be an aqueous solution and the carrier fluid may be oil. The figure below from the Ismagilov Patents depicts the formation of droplets in this manner:



'193 patent at Fig. 10A. The plug fluids are introduced in channels 10, 11, and 12, and droplets of plug fluids are created upon interaction with the oil that is flowing

through the perpendicular channel. The droplet volumes are typically in the picoliter to nanoliter range, but may be as small as a few femtoliters. *See id.* at 19:45-57.

While microfluidic systems and microfluidic droplets had long been known, researchers had not successfully used droplets as “microreactors” for chemical reactions. Given their tiny size, microfluidic droplets have a far higher surface to volume ratio than vessels previously used for carrying out chemical reactions. Carrying out chemical reactions on this minuscule scale and in the environment of a microfluidic droplet presented a host of unique problems inapplicable to bulk scale chemical experiments. Thus, while those in the field dreamed that chemical reactions could one day be carried out in microfluidic droplets, until the Ismagilov Patents, microfluidic droplets had only been used for rudimentary applications, such as sorting of particles.

The Ismagilov Patents presented a range of innovations in microfluidics, the combination of which overcame problems that had previously prevented researchers from using microfluidic droplets as chemical reactors and discouraged them from this approach. For instance, the Ismagilov Patents present techniques for overcoming at least the following historical problems:

- Dispersion of solutes in microfluidic devices that increased reagent consumption and prevented experiments or

measurements over long time scales (*e.g.*, minutes to hours).
See '193 patent at 11:54-62.

- Difficulties in preparing and controlling complex microfluidic droplets containing a mixture of reagents with precise compositions. *Id.* at 33:27-29; *see also id.* at 18:38-19:6.
- Unresolved issues associated with microfluidic channel substrate material and carrier fluids that caused droplet material to adhere to channels walls. *See id.* at 20:59-21:20.
- The inability to quickly mix reagents in droplets, which precluded the study of reactions that take place on short time scales. *See id.* at 11:64-67; 22:1-27:5.
- The inability to accurately optically detect and monitor reaction products due to measurement distortion introduced by carrier fluid interference. *See id.* at 29:62-30:4.
- Pronounced surface chemistry problems at the droplet/carrier-fluid interface in the high surface-to-volume environment of a droplet that led to adsorption of reagents and environments incompatible with biological molecules. *See id.* at 35:59-36:8.

The Ismagilov Patents include numerous exemplary techniques for fabricating microfluidic devices with complex structures, creating plugs, varying the concentrations of reagents in plugs, manipulating (*e.g.*, splitting and merging) plugs, and monitoring and analyzing the composition of plugs so that researchers could, for the first time, use microfluidic droplets as chemical reactors. *See id.* at 61:16-69:8. The Ismagilov Patents further include examples demonstrating a range

of different chemical reactions and phenomena that could, for the first time, be carried out using microfluidic droplets, including autocatalytic reactions (such as PCR), enzyme kinetics, RNA folding kinetics, synthesis of nanoparticles, and protein crystallization. *See id.* at 67:13-78:6. The research and development of these techniques and applications were reported in a series of frequently-cited (over 4,000 times) publications that came from the Ismagilov research group.

Each of the Ismagilov Patents includes claims directed to specific aspects of the described techniques for carrying out chemical reactions in microfluidic droplets. The '193 patent specifically includes claims directed to preparing droplets (“plugs”) of aqueous fluid substantially surrounded by an oil flowing through a microfluidic channel. *Id.* at claim 1. The claimed microfluidic system requires at least two channels: one for oil and another for carrying **both** a substrate molecule and reagents. *Id.* The formed plugs thus include at least one substrate molecule (such as a DNA or RNA molecule) and reagents for conducting an autocatalytic reaction, for example a PCR reaction. *Id.* at claim 1, 3. Dependent claims add further structural requirements related to carrying out reactions in droplets, including, for instance, the use of fluorinated oil (claim 6), the use of a surfactant in the carrier fluid (claim 7), the ability to trap plugs (claim 11), and methods for mixing reagents in droplets (claims 12-14).

C. The References Cited In The Petition

The Petition relies on various combinations of the following three references:

1. Ex. 1021, U.S. Patent No. 6,033,880 (filed Feb. 23, 1998) (hereinafter “Haff”).
2. Ex. 1004, U.S. Patent Application Publication No. 2002/0058332 (filed Sept. 14, 2001) (hereinafter “Quake Pub”) and Ex. 1005, U.S. Provisional Patent Application No. 60/233037 (filed Sept. 15, 2000) (hereinafter “Quake Provisional”).
3. Ex. 1006, U.S. Patent No. 6,524,456 (filed Sept. 29, 1999) (hereinafter “Ramsey”).

A brief summary of the references relied upon in the Petition is provided below as relevant background for understanding why the obviousness grounds presented in the Petition are unsustainable.

1. Haff Is A Capillary PCR Device That Is Unrelated To Microfluidics

The Petitioner’s “primary reference” is Haff. Petition at 1. The Haff references describes an “[a]pparatus and method for performing a nucleic acid amplification reaction and preferably a polymerase chain reaction (PCR) in a reaction mixture in at least one capillary tube.” Haff at Abstract. As Haff acknowledges, techniques for carrying out PCR in capillary tubes had been known since the late 1980s. *Id.* at 2:7-22. Thus, Haff pertains to a family of techniques

that were well-known and had been available long before the inventions described in the Ismagilov Patents. Microfluidics represented a breakaway from such techniques.

According to Haff, a problem with prior art capillary tube PCR machines was that the volume of the reaction was limited to about “10 microliters to 1.5 milliliters.” Haff at 2:23-24. Haff explains that it “is hard to scale up these volumes.” *Id.* at 2:27. Haff purports to provide a capillary tube PCR instrument that, unlike the prior art, allows one to **increase** the volume of a PCR reaction. *See, e.g., id.* at 7:27-30 (“The first embodiment is designed for preparative scale PCR with volumes upward of about 1 milliliter with no set upper bound other than potentially the maximum volume of the reaction tube loop.”); *id.* at 11:1-3 (“The principal advantage of the second embodiment shown in FIG. 2 is the large volume of amplified product that can be obtained in one pass.”); *id.* at 15:51-54 (“An excellent advantage of the instrument shown in FIG. 5, as with many other of the capillary tube PCR instruments disclosed above, is the ability to scale up the volume of finished product produced....”).

Focused on techniques for **increasing** the volume of a PCR reaction in capillary tube, Haff teaches against the fundamental idea behind microfluidics. Indeed, Haff uses capillary tubes with size on the order of “1 mm to 2 mm in internal diameter.” Haff at 3:8-9. The Petitioner’s expert acknowledges that this

size is inconsistent with what one of skill in the art would expect of a microfluidic device. Ex. 1002 ¶ 65. Since Haff is not a microfluidic device, there are of course no microfluidic droplets.

Rather, in Haff, PCR is purportedly carried out by forcing a bulk PCR reaction mixture through a capillary tube which is routed through alternating hot and cool zones. *See, e.g.*, Haff at Fig. 2. By this mechanism, Haff supposedly avoids having to repeatedly change the temperature of a large thermal mass to cycle the PCR reaction mixture. *See id.* at 5:12-20. Haff requires the use of hot and cool zones thermally separated from one another; a large thermal gradient must be maintained between the hot and cool zones. This is accomplished by physically separating the hot and cool zones or a by introducing an insulating thermal barrier between these zones. *See, e.g., id.* at 7:36-38. The embodiments of Haff based on this approach preferably use denaturation times of 5–15 seconds and annealing/extension incubation times of up to several minutes. *Id.* at 7:67-8:3; *see also id.* at 7:16-18.

2. Quake Teaches The Use Of Microfluidic Droplets For Sorting

Unlike Haff, Quake is directed to a microfluidic system. In particular, the Quake is directed to the use of microfluidic droplets for *sorting* particles. *See, e.g.*, Quake Pub ¶ 12 (“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.* ¶ 4 (“In a preferred embodiment, the devices and methods of the invention are used to sort or evaluate virions or virus particles. Other preferred embodiments are used to sort or evaluate molecules, such as nucleic acids or proteins, or cells, such as bacteria or pathogens.”). The word “sorting” (or some variation thereof) appears 274 times in Quake.

According to Quake, the invention provides an alternative to FACS and flow cytometry, which had been previously used for sorting biological particles. Quake purports to address the problems associated with FACS and flow cytometry, which are detailed at ¶¶ 7-11 of Quake. *See, e.g., id.* ¶ 7 (“Conventional flow sorters, such as FACS have numerous problems that render them impractical for analyzing and sorting viruses and other similarly sized particles.”).

While Quake mentions the possibility of reactions in passing, it does not teach methods for carrying out autocatalytic chemical reactions in microfluidic droplets. PCR, for instance—the reaction upon which Petitioner bases its reliance on Quake in relation to the ’193 patent claims—is rarely mentioned in Quake. The primary discussion of PCR comes in the Background of the Invention, where PCR is criticized as an inadequate tool for “detect[ing] viral DNA or RNA directly in clinical specimens.” *See* Quake Pub ¶ 6.

In Quake, “[d]roplets of aqueous solution containing viral or other particles”

are formed. *Id.* ¶ 12. This is done by introducing a flow of a fluid that may “contain a biological sample (e.g., molecules of an enzyme or a substrate, or one or more cells, or one or more viral particles)” into a main channel through which a fluid is flowing that is immiscible with the first fluid. *Id.* ¶ 15. After the droplets are formed, Quake teaches that they are directed to a “discrimination region,” where “cells or virions can change direction to enter one or more other channels, e.g., a branch channel, depending on a signal received in connection with an examination in the detection region.” *Id.* ¶ 71. Particles are thus sorted. All the examples in the specification are directed to the fabrication and implementation of microfluidic devices for *sorting* based on the above concept.

3. Ramsey Teaches A Primitive Microfluidic Device

Ramsey discloses a primitive microfluidic device, and teaches a technique for moving small volumes of liquids. It does not teach or use microfluidic droplets. Rather, Ramsey discloses electrokinetic transport to introduce alternating volumes of “transport fluid” and “segmenting fluid” through a microchannel. Ramsey does not state what the “transport fluid” is composed of, although it is ostensibly aqueous. As to the nature of the “segmenting fluid,” Ramsey offers no working examples and hence few specifics. Rather, Ramsey suggests a number of possibilities for the “segmenting fluid,” including paraffin, mineral oils, perfluorocarbons, silicon oils, and even propane gas. *See* Ramsey at 6:44-56.

D. The Person Of Ordinary Skill In The Art

According to the Petition, one of ordinary skill in the art would have already known how to perform chemical and biological analysis in microfluidic devices, and would have already had two years of experience in creating such devices. Petition at 3. The Petition further attempts to imbue the skilled artisan with knowledge in the fields of “fluid dynamics, microscale reactions, chemistry, biochemistry, and mechanical engineering” and the knowledge of several members of a “multidisciplinary team.” *Id.* at 3.

This dramatically overstates the level of skill in the art and misapprehends the state of microfluidics in the relevant time frame. The inventors on the Ismagilov patents were mostly graduate students. And, as late as 2006, researchers characterized microfluidics as a field in “infancy.” *See, e.g.*, Ex. 2009 [Whitesides, *Nature* 2006] at 372 (“So, what next for microfluidics? It is both a science and a technology. . . . 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.”).

Accordingly, in the 2002 time frame, the skilled artisan would have been a researcher interested in microfluidics with at least a bachelor’s degree in a hard science that involves both chemical and physical phenomena, such as chemistry, physics, chemical engineering, bioengineering, or mechanical engineering. Work related to the use of capillary systems had been ongoing since the 1950s and was

widely accepted. *See* Petition at 2-3. Accordingly, the skilled artisan interested in analyzing biological and chemical samples would have most likely attempted to follow these tried and true techniques. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (“A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art.”).

The skilled artisan would have viewed microfluidics as a breakaway from such techniques and would have understood that researchers had made only simple proof-of-concept demonstrations for microfluidic techniques related to introducing reagents and samples, moving fluids, and mixing fluids. *See* Ex. 2009 [Whitesides, *Nature* 2006] at 369 (describing “[t]he present” state of microfluidics in 2006). Because these techniques had not moved beyond proof-of-concept, these techniques would not have been routine to the skilled artisan, and their use in applications would not have been reflexive. *See id.* at 371 (“Above all, [microfluidics] must become successful commercially, rather than remain a field based on proof-of-concept demonstrations and academic papers.”).

Further, one of skill in the art would have understood microfluidics to be largely limited to continuous flow microfluidics, as opposed to droplet microfluidics, which was barely in the proof-of-concept stage. As of 2002, the skilled artisan would have had little, if any, experience with microfluidic droplets because the field was still considered nascent as of 2008. *See, e.g.*, Ex. 2010 [Teh

et al., Lab Chip 2008] at 216 (“This paper provides a comprehensive review of the field of ‘droplet’ or ‘digital’ microfluidics and its applications. This nascent field has attracted a diverse group of researchers to study the fundamentals of two phase dynamics in microchannels and also to develop novel solutions for biological and chemical applications that are superior to conventional techniques.”).

III. CLAIM CONSTRUCTION

The Petition addresses seven claim terms, but only provides a concrete construction for two of them. For the other five terms, the Petition simply presents arguments regarding the breadth of the claim term and specific features it “would encompass.” Below, Patent Owner addresses specific errors in Petitioner’s claim construction arguments. All claim terms that are unaddressed have their plain and ordinary meaning. Patent Owner’s position regarding the scope of the claims under their broadest reasonable interpretation is not necessarily the appropriate scope of the claims under different claim construction standards or when different issues and evidence are presented.

A. “plugs of the aqueous fluid”

Petitioner contends that “plugs of the aqueous fluid” should be construed as “volumes of an aqueous fluid surrounded by a carrier fluid in which it is substantially immiscible, such as a non-polar or hydrophobic fluid, e.g., an oil, and the diameter of a plug is substantially similar to the cross-section of the channel in

which it is formed and the aqueous fluid is separated from the channel wall by a thin film of carrier fluid.” Petition at 13. This is not the broadest reasonable interpretation of “plugs of the aqueous fluid.”

Petitioner’s proposed construction selectively imports non-essential attributes from the specification mistreating exemplary options as though they were definitional. For instance, Petitioner’s proposed construction requires plugs to be “separated from the channel wall by a thin film of carrier fluid.” No such requirement is stated anywhere in the description of plugs that appears in the specification. *See* ’193 patent at 9:27-60. As depicted in Fig. 33B, plugs may be separated from the wall of the channel by more than a “thin film” of carrier-fluid. Similarly, Petitioner’s proposed construction requires plugs to have substantially the same diameter as the channel in which they are formed. Yet, the specification states only that plugs “should” have this size when formed. *Id.* at 9:34-37. At the same time, the specification states that plugs “may vary in size,” and teaches that by “controlling the difference between the oil and water flow rates at the plug-forming region, the size and periodicity of the plugs generated may be regulated.” *Id.* at 9:34-47.

While Petitioner’s proposed construction attempts to limit the shape and environment of a plug, it ignores the very first thing the specification states about what a plug is. As the specification states, “[p]lugs’ in accordance with the

present invention are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible.” *Id.* at 9:27-30. Every single embodiment in the specification discloses the formation of plugs in this manner, making overwhelmingly clear that this is the defining attribute of plugs. *See, e.g., id.* at Figs. 2A-2, 5-6, 10A, 25A-C, 26A-B, 27B, 30, 44A-D, 45C-D, 46, 49, 51A-B, 52A-B, 54A-B.

Accordingly, the broadest reasonable construction of the term “plugs of the aqueous fluid” is “volumes of aqueous fluid formed when a stream of aqueous fluid is introduced into the flow of a substantially immiscible carrier-fluid.”

B. “conditions suitable for the autocatalytic reaction ... such that the at least one substrate molecule is amplified” ”

Petitioner contends that this term “would encompass at least providing a stimulus such as radiation, heat, temperature or pressure change, ultrasonic wave, or a catalyst to induce a reaction that gives rise to the transformation of the reagent to another reagent, intermediate, or product.” Petition at 14. Whether this term would “encompass” this or not, Petitioner’s description bears little relation to the original claim language and is not a claim construction at all. It is an unsupported attempt to read the claims on to the prior art Petitioner has identified. Indeed, Petitioner apparently seeks to broaden the claims to cover any system in which a broad range of stimuli may be provided, regardless of whether the conditions

necessary for a successful autocatalytic reaction (including PCR) in droplets are present, including the proper pH, the correct buffers and salts, and the right reagents. Importantly, Petitioner's proposed "construction" ignores that the provision of a single stimulus such as those listed in the Petition would not necessarily, in itself, be sufficient to induce an autocatalytic reaction in a microfluidic plug.

Due to the high surface-to-volume ratio of a microfluidic droplet, there are additional unique issues that must be addressed in seeking to conduct autocatalytic reactions (such as PCR) in droplets, including unwanted adsorption of proteins on at the surface of the droplet/carrier-fluid interface. *See infra* pp. 43-44. This is explained in the '193 patent:

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. Polyethylene glycols (PEG) and oligoethylene glycols (OEG) are known to reduce non-specific adsorption of proteins on surfaces.

'193 patent at 35:59-66. Subsequently, researchers have noted that careful choice of droplet conditions is "necessary to provide the droplets with enough stability to avoid exchange of their components, fusion, change of volume and aggregation in

the reservoir.” Ex. 2011 [Huebner et al., Lab on a Chip 2008] at 1248. “For biochemical experiments this becomes crucial as the active enzyme may lose activity due to constraints imposed by the [oil/water] interface.” *Id.*

Thus, to the extent Petitioner’s proposed construction is intended to merely require a single stimulus to induce an autocatalytic reaction (regardless of whether the provision of that single stimulus is sufficient to induce the reaction), it must be rejected. The skilled artisan would understand that this term refers not just to the provision of a stimulus, but to a global set of physical and chemical conditions that allows one to conduct an autocatalytic reaction (including PCR) in droplets.

IV. REASONS WHY THE PETITION SHOULD BE DENIED

A. Petitioner’s Expert Witness Declaration Is Entitled To No Weight

Petitioner’s expert witness declaration is no more than a carbon copy of the Petition. Paragraphs 14-20, 22-46, and 53-134 of the declaration track pages 2-11, 11-17, and 20-54 of the Petition nearly verbatim in prose, structure, and substance. While Petitioner has made some cosmetic changes, the only substantive differences are the expert’s qualifications, legal standard, a background discussion of PCR, and the absence of an opinion on licensing. Throughout, the Petition cites to expert witness testimony that is largely conclusory and that merely repeats the arguments of the Petition—in the very same order and using mostly the same language. *See, e.g.*, Petition at 4-6 (citing ¶¶ 16-19 of declaration in order).

“Merely repeating an argument from the Petition in the declaration of a proposed expert does not give that argument enhanced probative value.” *Kinetic Techs., Inc. v. Skyworks Solutions, Inc.*, IPR2014-00530, Paper No. 8 at 13 (Sept. 29, 2014). Accordingly, an expert declaration that “only mirror[s] the corresponding text of the Petition and do[es] not provide any factual basis for their assertions” is “entitled to little weight.” *Atoptech, Inc. v. Synopsys, Inc.*, IPR2014-01160, Paper No. 9 at 15 (Jan. 21, 2013). The Petition’s reliance on facsimile and conclusory expert witness testimony is reason enough for the Petition to be denied, and portends the presence of further substantive deficiencies in the Petition.

B. Key Claim Elements Are Not Taught In The Cited Art

Petitioner’s argument that the combination of Haff and Quake renders the ’193 patent’s claims obvious fails for ignoring a central tenet of the obviousness analysis under § 103: The elements of the claim in question must be found to be *available* in the prior art as a threshold step in the obviousness analysis. *Shopkick, Inc. v. Novitaz, Inc.*, IPR2015-00279, Paper No. 7 at 30 (May 29, 2015) (citing KSR, 550 U.S. at 418). Where, as here, the cited prior art fails to teach all the elements of the claim, the Board regularly declines to institute IPR. *See, e.g., Google, Inc. v. Simpleair, Inc.*, IPR2015-00179, Paper No. 11 at 16 (Apr. 17, 2015); *Apple, Inc. v. Memory Integrity, LLC*, IPR2015-00161, Paper No. 18 at 16 (May 8, 2015); *Micron Tech., Inc. v. MLC Intellectual Prop., LLC*, IPR2015-

00504, Paper No. 8 at 14 (July 20, 2015); *C.R. Bard, Inc. v. Medline Indus., Inc.*, IPR2015-00509, Paper No. 11 at 12 (July 15, 2015).

1. Haff And Quake Do Not Teach Conditions Suitable For A Polymerase-Chain Reaction In A Plug

The claims of the '193 patent require “providing conditions suitable for the autocatalytic reaction (including PCR, which is recited in claim 3) in the at least one plug such that the at least one substrate molecule is amplified.” ’193 patent at 78:27-29. Neither Haff nor Quake teaches this element.

Haff does not teach this element for the simple reason that it does not teach microfluidic plugs (*i.e.*, droplets). Nowhere does Petitioner contend that Haff teaches droplets. Because Haff does not teach droplets, it cannot possibly teach the conditions necessary for carrying out an autocatalytic reaction (including PCR) for amplification of a substrate molecule in the high surface-to-volume environment present “in a plug.” Quite the opposite, Haff addresses PCR in capillary tubes, where the surface-to-volume ratio is at least an order of magnitude less than in a droplet and where the enzymes and reagents do not interact with a carrier fluid. *See infra* n.6; *supra* Part II.C.1; *infra* Part IV.C.1. As explained below, conducting enzymatic reactions in the environment of a droplet presents unique considerations pertaining to the interaction of the enzyme and reagents with the carrier fluid at the surface of the droplet. *See infra* pp. 43-44, 55-58. Because Haff is focused on a

system completely different from a microfluidic droplet, it does not teach this claim element.

Neither does Quake provide this claim element. The only thing Petitioner points to in Quake as allegedly teaching this is a single sentence stating “[m]icrofabrication permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR.” Petition at 30 (citing Quake Pub ¶ 80). At best, this sentence discloses that PCR (and “other technologies”) might be done on a microfabricated chip. But it does not teach or suggest conditions suitable for carrying out an autocatalytic reaction (including PCR) in a plug. Quake cannot possibly be teaching this because, as explained above, Quake is focused on providing an alternative to PCR, not a better way of doing PCR. *See supra* Part II.C.2.

2. Haff And Quake Do Not Teach A Channel For At Least One Substrate Molecule and Reagents For Conducting an Autocatalytic Reaction And A Second Channel Through Which An Oil Is Flowed

Neither Haff nor Quake teaches the use of two channels in which one channel flows an aqueous fluid containing a substrate molecule and reagents for an autocatalytic reaction and the second channel flows an oil. Rather, both references teach wholly different methods.

As Petitioner concedes, rather than teaching the use of two channels, one

containing a substrate and reagents and the other containing an oil, Haff teaches a method of “*alternatively injecting*” aqueous fluid containing reagents and then immiscible fluid. Petition at 36. Petitioner cites Haff for its disclosure that a syringe is used to move a reaction mixture through a *single* channel in a capillary system. Haff at 10:23-28. But that citation includes no teaching of two separate channels. Rather, as Petitioner concedes, Haff discloses “a main channel,” and Petitioner points to nothing in Haff that discloses a second channel. Petition at 31-32. Petitioner’s claim chart does not even cite to Haff for the requirement that there be at least two channels in the microfluidic system. *Id.* at 22-23 (citing only Quake for the requirement of “at least two channels”). Indeed, the figure upon which Petitioner relies to disclose elements of Claim 1 clearly shows only a single channel. *See id.* at Fig 2.

As to Quake, Petitioner points to nothing in Quake that teaches the use of one channel in which an aqueous fluid containing a substrate molecule *and* reagents for an autocatalytic reaction flow. *See* Petition at 23-25. As Petitioner’s own citations show, Quake teaches forming droplets containing only a single biological molecule, without a reagent. Quake Pub ¶ 120 (“In particular, the sample concentration should be dilute enough that most of the droplets contain no more than a single molecule, cell or virion, with only a small statistical chance that a droplet will contain two or more molecules, cells or virions.”). This is critical to

Quake’s method, which is designed to sort these molecules based on identifiable characteristics. While Quake provides abstract discussions of droplets containing reactive substances, these droplets are formed only through droplet mergers. *Id.* ¶ 119. Thus, Petitioner has failed to show that Quake teaches the use of a channel containing a substrate and reagents for performing an autocatalytic reaction.

C. Ground 1: The Combination of Haff And Quake Does Not Render The Claims Obvious

1. Haff Is Not Analogous Art

“A reference qualifies as prior art for an obviousness determination under § 103 only when it is analogous to the claimed invention. Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor’s endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.” *In re Klein*, 647 F.3d 1343, 1348 (Fed. Cir. 2011) (internal citations and quotations omitted). The Haff reference—which is the Petitioner’s “primary reference”—fails both of these tests. Petition at 1.

First, the Petition and expert declaration demonstrate that Haff is not from the same field of endeavor as the ’193 patent. The ’193 patent states throughout that it is directed to the field of microfluidic devices. *See, e.g.*, ’193 patent at

11:54-56 (“In one aspect of the invention, the various devices and methods according to the invention are used to overcome one or more of the following problems involving microfluidics.”); *see also id.* at 44:38-41; 45:5-8. Likewise, the claims of the ’193 patent are expressly directed to a microfluidic system.

Consistent with this, the Petition defines the person of ordinary skill in the art as one “in the field of microfluidic devices and the methods of using such devices.” Petition at 2; *see also id.* at 3 (“A POSA would have had knowledge of strategies for performing chemical and biological analysis in microfluidic devices.”). According to the Petition and Petitioner’s expert, a POSA would have had “two years of experience in using, designing or creating microfluidic devices.” *Id.*; Ex. 1002 ¶ 14. It is thus undisputed that the field of the ’193 patent is microfluidic devices.

Haff, however, is *not* in the field of microfluidic devices. While microfluidics is directed to the manipulation of *small* volumes of liquids, Haff is directed to the exact opposite problem of *increasing* the volume of a PCR reaction. As Haff states, the “PCR volume has been limited to a range of about 10 microliters to 1.5 milliliters in conventional heat block or liquid bath heat exchanger PCR....” Haff at 2:23-25. According to Haff, it “is hard to scale up these volumes.” *Id.* at 2:27. Thus, Haff describes embodiments that, for instance, are “capable of performing PCR on a reaction volume of any scale including

greater than about 1 milliliter.” *Id.* at 7:10-11. The principal embodiment of Haff relied upon in the Petition has as a “principal advantage” the capability of obtaining a “large volume of amplification product” in a single pass, thus obviating the need to carry out a series of smaller 100 microliter reactions, which must be tediously pooled and realiquoted. *Id.* at 11:1-9.

Petitioner’s expert acknowledges that Haff is not about microfluidic devices, but is instead directed to a system for dealing with “larger volumes” of fluids:

Additionally, Haff’s device and method uses larger volumes of PCR reaction mix than what would be required in a microfluidic PCR device because Haff’s capillary tubes have an internal diameter of about 1 mm to 2 mm.

Ex. 1002 ¶ 65. There is thus no dispute that Haff is outside the field of the ’193 patent.

Haff also is not reasonably pertinent to the problems being addressed in the ’193 patent. As the ’193 patent explains, the “various devices and methods according to the invention are used to overcome one or more of the following problems involving microfluidics,” including excess reagent consumption, the inability to monitor reactions over variable time scales, slow mixing of reagents, and the inability to control surface chemistry. *See generally* ’193 patent at 11:54-12:17. In solving these problems, the ’193 patent opened up a range of novel

applications. For instance, the micro-scale reaction techniques disclosed in the '193 patent allow for miniaturization of protein crystallization techniques (*id.* at 50:4-61:3), microscale kinetic studies of protein folding (*id.* at 37:7-28), and monitoring of autocatalytic reactions (*id.* at 66:45-67:12). Detailed examples of each of these techniques are set forth in the '193 patent.

Haff, however, discloses only a capillary PCR device to carry out PCR reactions on a large scale. *See supra*. This is the exact opposite of the micro-scale reactions that are the subject of the Ismagilov Patents. The fabrication, design, and structure of the capillary tube device in Haff bears no similarity to the etched microfluidic device in the '193 patent, and nothing in Haff teaches the types of applications that are detailed in the '193 patent. Likewise, nowhere does the '193 patent suggest that the capillary tube device of Haff—which dates back to the early 1990s—is of any relevance. Coming from a different field, focusing on a different purpose, and reflecting an irrelevant design, Haff is not a reference that “logically would have commended itself to an inventor’s attention.” *In re Klein*, 647 F.3d at 1343, 1348, 1352.

Because the Petition relies upon non-analogous art that is irrelevant to the invention of the '193 patent, the Petition suffers from a threshold deficiency and review should not be instituted. This threshold deficiency inherently leads to a cascade of additional deficiencies that provide yet additional reasons to deny

review.

2. One Of Skill In The Art Would Not Combine Quake And Haff And The Petition Does Not Establish A Reasonable Expectation Of Success

An invention is sometimes obvious in view of prior art patents when “a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.” *KSR Int’l v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007). The Quake and Haff references, however, come from disparate fields and have different objectives. As a natural consequence, Quake and Haff do not fit together at all, and one of skill in the art would not have thought to combine them. Nor would such a person have had a reasonable expectation of successfully doing so. Thus even if the Board were to conclude that Haff meets the threshold analogous art standard, review still should not be instituted.

a. The Petition’s “Problem With A Solution” Rationale Is Legally Deficient And Based Upon Mischaracterizing The Art

“Petitioner must show some reason why a person of ordinary skill in the art would have thought to combine particular available elements of knowledge, as evidenced by the prior art, to reach the claimed invention.” *Shopkick, Inc. v. Novitaz, Inc.*, IPR2015-00279, Paper No. 7 at 30 (May 29, 2015) (citing *KSR*, 550 U.S. at 418). When an obviousness challenge in an IPR petition is insufficiently supported by such reasoning, the Board regularly declines to institute review. *See*,

e.g., *Cisco Sys., Inc. v. Constellation Techs.*, IPR2014-01179, Paper No. 7 at 13-16 (Feb. 4, 2015); *Google, Inc. v. EveryMD.com LLC*, IPR2014-00347, Paper No. 9 at 20-27 (May 22, 2014); *Gracenote Inc. v. Iceberg Indus., LLC*, IPR2013-00551, Paper No. 6 at 31-33 (Feb. 28, 2014).

The purported motivation to combine presented in the Petition is that Haff suffers from flaws (*e.g.*, usage of a large amount of reagents and cross-contamination arising from adherence of reagent to channel walls) that might be remedied by using Quake’s microfluidic system. *See* Petition at 31. According to the Petition, “using Quake’s method of making microfluidic droplets of aqueous fluid would diminish the drawbacks of Haff’s slug adherence to channel walls and reagent diffusion.” *Id.* at 34. However, “knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method.” *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008). This case vividly illustrates that difference.

In Haff, slugs are separated from one another by air or fluid. While attempting to paint slug cross-contamination as a major problem, the Petition nonetheless acknowledges that Haff’s separation of slugs by air or fluid could “minimize” the “cross-contamination” issue. Petition at 5. Indeed, the Skeggs patent that is relied upon in the Petition reported that this was so as early as 1957:

It will be understood that in the course of the travel of this segmented

fluid stream through tube 47, the segments of air displace liquid from the inner surface of the tube so as to prevent or substantially reduce the mixing of the samples with each other and hence prevent the contamination of one sample by another in the operation of the machine for analyzing a series of samples.

Ex. 1008 at 4:42-48. The 1969 Smythe patent (also relied upon in the Petition) confirmed that this mechanism had “been successfully utilized to reduce this intersample contamination,” Ex. 1010 at 1:59-61, and reported that it could be ameliorated even further by using Teflon channel walls wetted with a silicone film. *Id.* at 2:53-55 (“The aqueous sample segments do not touch this inner wall of the conduit, but, rather, travel within the film of silicone.”). Against this backdrop, the Haff reference never even mentions adherence of reagents to the walls or slug cross-contamination, and the Petition’s heavy reliance on these alleged “drawbacks” is thus dubious at best.

Nevertheless, the Petition asserts that these “drawbacks” would have been so severe that one of skill in the art would have been driven to overcome numerous technical challenges and re-engineer Haff as a microfabricated droplet device, in

the process changing the fundamental principles upon which Haff operates.³ The Petition fails to explain the mental process that would have led a person of ordinary skill in the art to take this dramatic and unjustified step. In other words, the Petition's analysis is based purely on hindsight.

Indeed, the Petition never explains why someone would not have addressed the alleged cross-contamination problem by simply wetting the capillary tubes with silicone, as proposed by Smythe in 1969. In fact, this is the very solution that Quake proposes. *See* Quake Pub ¶ 94 (“To prevent material (e.g., cells, virions and other particles or molecules) from adhering to the sides of the channels, the channels (and coverslip, if used) may have a coating which minimizes adhesion.”). Thus, even assuming there were some residual—and entirely unmentioned—cross-contamination problem in Haff, the cited art demonstrates that the skilled artisan would have either done nothing or taken far less drastic measures.

The Petitioner's assertion that one of skill in the art would have combined Quake with Haff because it might conserve reagents is also unpersuasive. Miniaturizing Haff as a microfluidic device is directly at odds with Haff's stated

³ These technical challenges are substantial and are detailed below in connection with Patent Owner's explanation for why Petitioner fails to establish a reasonable expectation of success. *See infra* Part IV.C.2.b.

advantage of being able to “scale up” the output of a PCR reaction. *See supra* Part II.C.1. In Haff, the use of large volumes of reagents is a virtue, not a drawback. It is difficult to understand why one of skill in the art would have been motivated to re-engineer a system designed to increase output as a microfluidic device that would then suffer from major output constraints. Nevertheless, even if reagent conservation were seen as a benefit of combining Quake and Haff, mere identification of a possible end-benefit does not substitute for a reasoned explanation for why the substitution would have been obvious. *See, e.g., Kaspersky Lab, Inc. v. Uniloc USA, Inc.*, IPR2015-00178, Paper No. 10 at 8-11 (April 21, 2015).

The factual and logical disconnects between Petitioner’s proposed motivation to combine and the teachings of the art demonstrate that Petitioner’s proposed motivation to combine is nothing more than a hindsight-driven litigation theory. The Petition repeatedly lapses into mischaracterization of the art in an attempt to support this misguided theory.

For instance, the Petition asserts that “Quake acknowledges the drawbacks of methods that are like those disclosed in Haff, which include diffusion or mixing of reagents between slugs and slug adherence to channel walls.” Petition at 33. Similarly, the Petitioner’s expert asserts that “Quake acknowledges the problem of cross-contamination during the analysis of biological samples by PCR.” Ex. 1002

¶ 66. These arguments mischaracterize Quake.

Quake mentions PCR—the only autocatalytic reaction cited by Petitioners—only briefly, and primarily for the purpose of explaining how his technique is an *alternative* to PCR, not a better way of doing PCR. *See* Quake Pub ¶ 6. Quake *never* mentions capillary device systems such as Haff and nowhere suggests that Quake’s system is directed to overcoming whatever problems such devices might suffer from. Rather, Quake explains at length that it is directed to overcoming problems associated with traditional machines used for cell sorting and separation, in particular FACS and flow cytometry machines. *See* Quake Pub ¶¶ 7-11; *id.* ¶ 14. (“The microfabricated device and methods of the invention offer several advantages over traditional flow cytometry devices and methods.”). For instance, relative to traditional flow cytometry and FACS, Quake purportedly offers increased sensitivity, avoids the need for hydrodynamic focusing, avoids the need for charged droplets, reduces costs, obviates the need for cleaning and sterilization, avoids orifice clogging, and avoids material diffusing or exchanging positions. *Id.* While the Petition attempts to characterize Quake as addressing the problems of Haff that arise from the use of slugs in capillary tubes, neither FACS nor flow cytometry uses slugs and neither technique suffers from the problems identified in the Petition.

As another example, Petitioner asserts that “Haff (GEN1021) and Quake

(GEN1004) are both directed to performing enzymatic reactions, such as PCR, an autocatalytic reaction in small volumes of aqueous fluids.” Ex. 1002 ¶ 55. This is wrong.⁴ Haff is directed to *increasing* the volume of PCR reactions, not PCR in “small volumes.” *See supra* Part IV.C.1. And Quake is not directed to performing enzymatic reactions at all, let alone enzymatic reactions in droplets. Quake states repeatedly that it provides a technique for sorting particles that is an alternative to FACS or flow cytometry. *See* Quake Pub at Abstract (“A microfluidic device for analyzing and/or sorting biological materials....”); *id.* ¶ 12 (“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.* ¶ 113 (“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.

Autocatalytic reactions, by contrast, are rarely mentioned in Quake. The only autocatalytic reaction discussed at all in Quake is PCR. Quake primarily

⁴ Even if this assertion were correct, “Petitioner’s contention that the references solve the same need is better characterized as a contention that the references are analogous art than as a rational underpinning for the proposed combination.” *Microsoft Corp. v. Secure Web Conference Corp.*, IPR2014-00745, Paper No. 12, 14, (Sept. 29, 2014).

discusses PCR to describe its disadvantages as a diagnostics tool, thus setting the stage for describing microfluidic sorting as an *alternative* to PCR:

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.

Id. ¶ 6.

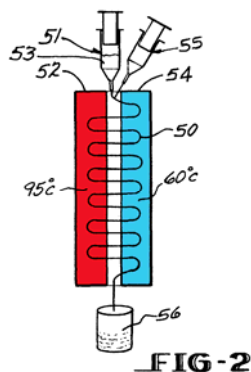
The only other mention of PCR in Quake comes in a single throw-away sentence where PCR is listed among a laundry list of other possibilities: “Microfabrication permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR (13), moving cells using optical tweezer/cell trapping (14-16), transformation of cells by electroporation (17), μ TAS (18), and DNA hybridization (5).” *Id.* ¶ 80. This sentence does not, as Petitioner’s expert asserts, “explicitly teach[] that [Quake’s] device and method can be integrated with PCR.” Ex. 1002 ¶ 75. It simply points out that it is a possibility for “microfabrication.”

b. The Petition Does Not Establish That One Of Skill In The Art Would Have Had A Reasonable Expectation Of Successfully Mixing Quake And Haff

In a nutshell, the Petition’s obviousness argument is that one of skill in the art would have replaced the capillary tubes of Haff with the microfluidics machinery of Quake to arrive at the claimed invention. For instance, the Petition asserts that it would have been “routine” to “adapt Haff’s capillary PCR device to use Quake’s method of creating encapsulated plugs comprising a target DNA sequence—*i.e.*, a substrate molecule— and PCR specific reagents—*i.e.*, reagents for conducting an autocatalytic reaction—to perform PCR in a microfluidic device.” Petition at 35-36. This is not so. The allegedly “routine” modification suggested in the Petition calls for one to abandon the single-channel principles upon which Haff operates and would require overcoming numerous engineering challenges. For over a half-century, the law has been clear that this fact pattern weighs against 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.

Here, the required changes are so substantial and raise so many challenges that the skilled artisan would not have had a reasonable expectation of successfully combining Quake and Haff. As the Petition states, the capillary PCR device of Haff uses a capillary tube that is routed “in and out of hot and cold sources of the

appropriate temperature.” *See* Petition at 30 (quoting Haff at 1:12-15). This is depicted in the figure below, which shows the capillary tube passing seven times from the cool side (depicted in blue) to the hot side (depicted in red):



In Haff, both the hot and cool zones are described as being liquid baths, and there is a gap between the two baths so that they do not come into thermal contact. *See* Haff at 9:65-10:6.

In Quake, however, the microfluidic channels are created by etching a groove into the surface of a wafer. *See* Quake Pub ¶¶ 133-39; Figs. 1A-1D. Accordingly, the channel is integrated into a single substrate. Because the entire channel is carved from a single substrate, there cannot be a thermal insulator between different portions of the channel, nor could one introduce an air gap between different portions of the channel. Thus, the techniques used in Haff for creating isolated thermal zones—as required for PCR in the technique of Haff—cannot be straightforwardly applied when the microfluidic channels of Quake are used. *See, e.g.*, Haff at 7:36-38.

Indeed, because the microfluidic device of Quake uses channels that are orders of magnitude smaller than those in Haff, one would need to maintain a thermal gradient over correspondingly smaller distances if one were to try and combine Quake with Haff. Quake, however, includes no teaching as to how to do this. Quake is focused solely on sorting of particles, and is thus completely unconcerned with how one would maintain thermally isolated zones in a microfluidic environment. One of skill in the art, with Quake and Haff in hand, would have no guidance whatsoever as to how this could be accomplished. In fact, as of 2007, this remained an active research issue, demonstrating that it would not have been seen as a routine or trivial. *See, e.g.,* Ex. 2012 [Zhang and Xing, Nucleic Acids Research, 2007] at 4229 (“Thermal interaction or ‘crosstalk’ has emerged as an important issue as chip device size decreases.”).

Yet another disconnect between Quake and Haff is that Quake uses droplets while Haff uses a bulk reaction mixture, which presents its own set of issues. While it is straightforward to include all necessary reagents for an autocatalytic reaction such as PCR in a bulk reaction mixture, consistently packaging all of these reagents into microfluidic droplets at the right concentrations is a much different matter. Quake, focused solely on sorting particles, teaches nothing about this. The Ismagilov Patents, on the other hand, include pages of teaching about how to form plugs, mix reagents in plugs, and vary the concentrations of reagents in plugs. *See,*

e.g., '193 patent at 17:24-27:5, 33:26-35:9.

The use of droplets introduces additional issues related to flow rate and the residence time of the droplets in the device. To generate droplets, one utilizes a continuous flow of a carrier fluid that intersects the flow of a “plug fluid.” Droplets are born from the flow of these fluids, and they are transported with the carrier fluid. Although Quake does not state the flow rate, contemporaneous technical literature by the inventors of Quake reports a flow rate of 6.4 cm/sec, and a similar droplet velocity (5.0 cm/sec) is reported in the Ismagilov Patents. *See* Ex. 1018 [Thorsen et al., PRL 2001] at 4165; '193 patent at 63:49-52.

This creates an immediate problem for one seeking to jimmy-rig Haff with Quake. In Haff, PCR extension times vary, but for embodiments based on the passage of a reaction mixture through alternating hot and cool zones, they may be minutes in length. Haff at 7:16-18, 7:67-8:3. In Figure 2 of Haff, there are seven extension cycles (*i.e.*, seven passages of the reaction mixture through the cool zone). Assuming seven cycles, and conservatively assuming 60 second extensions per PCR cycle, a microfluidic droplet moving at 5.0 cm/sec would travel 21 meters during the course of a PCR reaction ($60 \text{ sec} \times 5.0 \text{ cm/sec} \times 7 \text{ cycles} = 21 \text{ meters}$). This means that to use Quake with Haff, one would need to carve a channel roughly 21 meters long into a tiny silicon wafer that is only a few centimeters square.

The Petitioner's own expert documented these sorts of issues in a 2010 review article, and identified problems associated with increasing channel length:

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. The most straightforward method for increasing the residence times is to simply increase the channel length. Unfortunately, delay lines lead to a proportional increase in back-pressure, disrupting droplet formation and causing delamination of poly(dimethyl siloxane) (PDMS) layers.

Ex. 2013 [Theberge et al., *Angew. Chem.* 2010] at 5854.⁵ While solutions to these issues were ultimately proposed, this was not a “routine” problem to overcome. Quake says nothing about these issues because it is focused solely on sorting, and Haff is not even a microfluidic system. The Ismagilov patents, on the other hand,

⁵ Notably, these sorts of issues are present not just with droplets, but with continuous flow microfluidic PCR devices as well. *See, e.g.*, Ex. 2012 [Zhang and Xing, *Nucleic Acids Research*, 2007] at 4225 (“The rate at which the PCR solution travels between different temperature zones is difficult to regulate, and thus most of the continuous-flow PCR systems lack the flexibility to regionally control fluid flow velocity so as to meet different PCR requirements.”).

teach a technique that uses “expansion channels” for trapping plugs and allowing reactions to take place over extended time frames. *See, e.g.*, ’193 patent at 3:20-22.

Finally, one of ordinary skill in the art would not ignore the surface chemistry and biocompatibility issues that result from the tiny volumes of microfluidic droplets and their relative large surface to volume ratios. The surface to volume ratio of a sphere goes roughly as $1/r$. Therefore, the surface to volume ratio of a microfluidic droplet is *at least* an order of magnitude greater than the surface to volume ratio of the reaction fluid in the capillary tubes of Haff.⁶ “Control of the surface chemistry is particularly important in microfluidic devices because the surface-to-volume ratio increases as the dimensions of the systems are reduced.” ’193 patent at 35:59-61. Further, while the reaction mixture of Haff is in contact with inert glass or plastic capillary tube material, the exposed surface of a tiny microfluidic droplet is in contact with the chemical carrier fluid. 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 allow droplets to flow smoothly.

⁶ This estimate was determined using the 60 micrometer channels reported in Quake and the 1-2 millimeter channels reported in Haff.

The Petitioner's expert acknowledged the importance of this issue in his 2010 review article, specifically citing the contribution of the Ismagilov group to solving this problem:

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. 2013 [Theberge et al., *Angew. Chem.* 2010] at 5852 (citing L. S. Roach, H. Song, R. F. Ismagilov, *Anal. Chem.* 2005, 77, 785). Notably, the oligoethylene-terminated surfactants identified by Petitioner's expert are the very molecules invented by Ismagilov's group and described in the Ismagilov Patents. *See* '193 patent at 36:38-59. While the unique surface chemistry issues associated with microfluidic droplets are dealt with at length in the '193 patent, *see id.* at 35:58-36:59, neither Quake nor Haff address such issues at all.

Simply put, those of skill in the art would not have had a reasonable expectation of successfully replacing the capillary tubes of Haff with the microfluidic droplet technology of Quake. Petitioner's contention that the combination of Quake and Haff would have been "routine" is undermined by the lack of any reasoned explanation in the Petition for why this combination would

have been successful. The Petition simply asserts that there would have been a reasonable expectation of success because Quake (1) purportedly teaches how to generate aqueous plugs having a single molecule and (2) notes that microfabrication permits PCR to be integrated on a chip. *See* Petition at 29, 34-35. The Petitioner's expert adds no further insight, parroting the Petition without any additional reasoning or evidence. *See* Ex. 1002 ¶ 73. The fact that Quake teaches these discrete points, however, does not establish that Quake could be successfully combined with Haff. The Petition's arguments on reasonable expectation of success amount only to "mere conclusory statements," not 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).

Entirely absent from the Petition is any explanation as to how one of skill in the art would combine Quake and Haff to reach the claimed invention, including an explanation as to how and why the one of skill in the art would modify and adapt the references to make the combination possible. Petitioner was obligated to provide such an explanation. *See, e.g., ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (affirming finding of non-obviousness 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.”). Obviousness analyses that omit such an explanation are “fraught with hindsight bias.” *Id.* Thus, where, as here, such an explanation is missing, the Board regularly declines to institute IPR. *See, e.g., Apple, Inc. v. Memory Integrity, LLC*, IPR2015-00172, Paper No. 16 at 16-17 (May 11, 2015) (denying institution where “neither Petitioner nor Dr. Horst explain how the directory board of Stanford DASH would be adapted to operate with point-to-point links, rather than a bus” and no reasonable expectation of success was established); *Daifuku Co., Ltd. v. Murata Mach., Ltd.*, IPR2015-00084, Paper No. 10 at 16 (May 4, 2015) (institution denied when petition was unsupported “by a specific engineering and technical analysis of how the asserted combination would have worked and why it would have been an obvious combination to one of skill in the art”).

D. Ground 2: One Of Skill In The Art Would Not Combine Quake And Haff With Ramsey

Claim 6 requires that the oil flowed in the second channel is “fluorinated oil.” The Petition acknowledges that Quake does not disclose this, but contends that one would combine Ramsey with Quake to satisfy this claim element.

Petitioner relies almost exclusively on a single sentence in Ramsey stating that “[p]erfluorocarbons may also be suitable because they are widely used where

biocompatibility is required.” Petition at 47. This is the *only* mention of perfluorocarbons in the entire Ramsey reference. Stating only that perfluorocarbons “may also be suitable” and mentioning them only once, Ramsey offers at most a mild and uncertain endorsement of perfluorocarbons as a segmenting fluid. At the same time, Ramsey points in numerous alternative directions, suggesting paraffin, mineral oils, silicon oils, and even propane gas as possible segmenting fluids. Ramsey at 6:36-56. This scattershot disclosure falls well short of demonstrating that it would be obvious to use perfluorocarbons in a microfluidic droplet system. “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).

Further, Ramsey is not even a droplet system. As such, it does not teach carrier fluids for droplets, nor does it address the unique issues associated with selecting a carrier fluid suitable for the high surface-to-volume environment of a droplet. *See supra* pp. 43-44. Accordingly, whatever Ramsey suggests about biocompatible segmenting fluids is by no means applicable to the selection of an appropriate carrier fluid for a microfluidic droplet system.

E. Secondary Considerations Demonstrate That The '193 Patent Is

Not Obvious

As documented above, Petitioner has failed to make a prima facie showing of obviousness under the cited prior art combinations. Even if Petitioner had made such a prima facie showing, however, secondary considerations must be taken into account. “Such objective evidence can establish that ‘an invention appearing to have been obvious in light of the prior art was not.’” *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)).

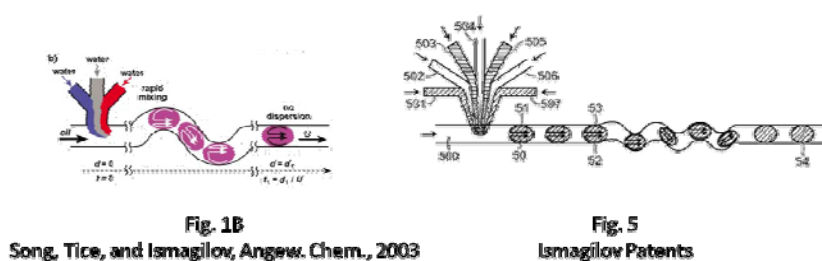
The Petition attempts to address evidence of secondary considerations that Patent Owner might submit. The Petition acknowledges that the Ismagilov Patents were licensed by RainDance and that RainDance’s RainDrop® system was named among the “Top Ten Innovations of 2014” by *The Scientist* magazine, but provides no persuasive rebuttal. More importantly, the Petition ignores the most palpable evidence of nonobviousness—the long felt need for methods of conducting biological reactions in droplets and the extensive praise that Ismagilov and co-workers received when they solved the problem.

1. Long Felt Need And Subsequent Praise

Dr. Ismagilov’s inventions include numerous novel elements, the overarching novel feature being the ability to use microfluidic droplets as compartmentalized microreactors. *See supra* Part II.A. The claims of the ’193

patent embody these novel elements, reciting methods for generating and using microfluidic systems for carrying out autocatalytic chemical reactions in droplets, or “plugs,” in microfluidic systems.” ’193 patent at 78:18-29.

The Ismagilov group’s research related to the claimed inventions was reported in a series of 2003-2006 publications authored by the named inventors of the Ismagilov Patents. Their first publication, a 2003 article in the journal *Angewendte Chemie* entitled “A Microfluidic System for Controlling Reaction Networks in Time,” reports techniques for generation of droplets, rapidly mixing reagents in droplets, and carrying out autocatalytic reactions in droplets. *See* Ex. 2014 [Song et al., *Angew. Chemie* 2003]. The techniques, figures, data, and results in this publication are those reported in the Ismagilov Patents. This is revealed, for instance, by a comparison of Figure 1B from the 2003 publication and Figure 5 of the ’148 patent:



Likewise, it is revealed by a comparison of Fig. 4 of the 2003 publication and Figure 7 of the ’193 patent:

Communications

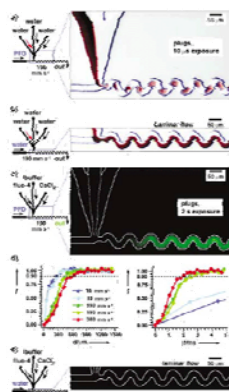


Fig. 4

Song, Tice, and Ismagilov, *Angew. Chem.*, 2003

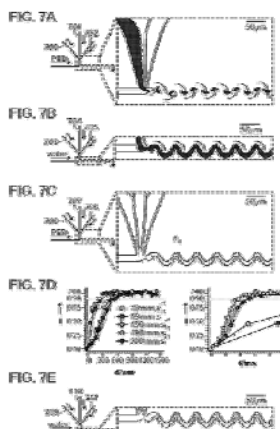


Fig. 7

Ismagilov Patents

This nexus is confirmed by the following claim chart, which compares claim 1 of the '193 patent to Ismagilov et al.'s 2003 and 2006 *Angewandte Chemie* papers:

Claim Text	Disclosure In <i>Angew. Chemie</i>
A method for conducting an autocatalytic reaction in plugs in a microfluidic system, comprising the steps of:	<p>“[M]icrofluidic system that . . . uses networks of microchannels. . . .” Ex. 2014 [Song et al., <i>Angew. Chemie</i> 2003] at 768.</p> <p>“A high surface-area-to-volume ratio ensures rapid heat transfer . . . and allows rapid switching between different temperatures. This rapid switching is essential for DNA amplification. . . .” <i>See also id.</i> at 7343.</p>
providing the microfluidic system comprising at least two channels having at least one junction;	<p>“[M]icrofluidic system that . . . uses networks of microchannels. . . .” <i>Id.</i> at 768.</p>
flowing an aqueous fluid containing at least one substrate molecule and reagents for conducting an autocatalytic reaction through a first channel of the at least two channels;	<p>“To form droplets from two solutions of reagents without bringing the reagents into prior contact we flowed these solutions in a microchannel . . . and used an inert center stream to separate them. These three streams were continuously injected into a flow of water immiscible perfluorodecaline (PFD) Emulsions . . . such as PFD . . . should be compatible with a range of</p>

Claim Text	Disclosure In Angew. Chemie
<p>flowing an oil through the second channel of the at least two channels;</p>	<p>biological molecules.” <i>Id.</i> at 769; <i>see also</i> Fig. 1(b).</p> <p>“We controlled the volumetric flow rates through each channel using syringe pumps. Dispersion was eliminated by localizing the reagents within aqueous plugs . . . separated by water-immiscible oil.” <i>Id.</i> at 768; <i>see also</i> 770 (plugs did not block 100-μm wide channel); Figure 5 (monodisperse droplets formed).</p> <p>“These three streams were continuously injected into a flow of water-immiscible perfluorodecaline (PFD)” <i>Id.</i> at 769; <i>see also id.</i> at Fig. 1(b).</p>
<p>forming at least one plug of the aqueous fluid containing the at least one substrate molecule and reagents by partitioning the aqueous fluid with the flowing oil at the junction of the at least two channels, the plug being substantially surrounded by an oil flowing through the channel, wherein the at least one plug comprises at least one substrate molecule and reagents for conducting an autocatalytic reaction with the at least one substrate molecule; and</p>	<p>“To form droplets from two solutions of reagents without bringing the reagents into prior contact we flowed these solutions in a microchannel . . . and used an inert center stream to separate them. These three streams were continuously injected into a flow of water-immiscible perfluorodecaline (PFD) Emulsions . . . such as PFD . . . should be compatible with a range of biological molecules.” <i>Id.</i> at 769; <i>see also id.</i> at Fig. 1(b).</p> <p>“We controlled the volumetric flow rates through each channel using syringe pumps. Dispersion was eliminated by localizing the reagents within aqueous plugs . . . separated by water-immiscible oil.” <i>Id.</i> at 768; <i>see also id.</i> at 770 (plugs did not block 100-μm wide channel); Figure 5 (monodisperse droplets formed).</p> <p>“This approach . . . is also compatible with . . . forming droplets with controlled concentrations of reagents.” Ex. 2015 [Song et al., Angew. Chemie 2006] at 7341.</p>
<p>providing conditions suitable for the autocatalytic reaction in the at least one plug such that the at least one</p>	<p>“A high surface-area-to-volume ratio ensures rapid heat transfer . . . and allows rapid switching between different temperatures. This rapid switching is essential for DNA amplification. . . .” <i>Id.</i> at 7343.</p>

Claim Text	Disclosure In Angew. Chemie
substrate molecule is amplified.	“Fluorinated surfactants can be used to control the surface chemistry at the liquid–liquid interface between the aqueous phase and the fluorinated phase.” <i>Id.</i> at 7343.

If the innovations reported in the Ismagilov group’s publications and patents were so obvious, one would have expected them to have received little attention and acclaim. Just the opposite happened. The Ismagilov group’s first 2003 publication has been cited nearly 450 times by researchers in the field. Ex. 2016 [SciSearch search report]. Similarly, two 2003 publications in the *Journal of the American Chemical Society* have each been cited nearly 400 times. A subsequent 2006 review article in *Angewendte Chemie*, “Reactions in Droplets in Microfluidic Channels,” has been cited almost 800 times. Ex. 2015 [Song et al., Angew. Chem. 2006]. In total, Dr. Ismagilov’s publications regarding his work on droplet-based microfluidics and performing reactions in such systems have been cited over 4,000 times. On the basis of his high citation impact scores, Thomson Reuters named Dr. Ismagilov one of the world’s top 100 most influential chemists during the period from 2000-2011. Ex. 2017 [Science Watch 2015].

Petitioner’s own expert cites the Ismagilov group’s work heavily in his own publications for establishing the utility of microdroplets for performing and monitoring chemical reactions. For instance, he cited this work for its teaching of a “unique platform” for miniaturizing chemical reactions and the benefits the

approach offered:

Microdroplets formed within microfluidic devices present a unique platform for the miniaturization of chemical and biochemical reactions.¹ The principal benefits lie in the ability to create nanolitre to femtoliter-sized individual reactors in which the contents can be accurately controlled.^{2,3} 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.^{4,5}

Ex. 2007 [Fidalgo, et al., Lab Chip 2007] at 984; *see also, e.g.*, Ex. 2018 [Huebner et al., Anal. Chem. 2008] at 3890 (citing multiple publications by Dr. Ismagilov's group).

The work of Ismagilov and co-workers has been specifically described as highly influential in advancing the microreactor field. The “seminal” impact of the work reported in their 2003 *Angewandte Chemie* publication was described in 2006:

Nonetheless, there is a clear need for simple design tools for heterogenous systems in microchannel reactors. Engineers need to be able [*sic*] schedule “microchannel unit operations” to exploit the promise of tight control for microchannel processing, to achieve high-thruput, parallel, and dense packed production or analysis. ***Thus, batches of reagents must be deliverable by microchannel transport, switchable on demand. (9) in a seminal paper has shown how to***

generate and then model mixing and reaction within single, isolated droplets, each one of which can be directed automatically due to precise knowledge of its current position. The generation mechanism entrains vorticity in the droplet, which then serves as a chemical micromixer following the analogy with the “baker’s transformation” as a mechanistic paradigm for chaotic advection (13). Helen Song, a colleague of Rustem Ismagilov, reported on this work during the CISM workshop. The success of their engineering leads to the obvious extension – if transported droplets can be treated as pseudo-batch reactors, under what circumstances can layered flows be treated as plug-flow tubular reactors, and are there other arrangements for the reaction engineering that permit droplets to be treated as batch reactors, in the frame of reference of the droplet?

Ex. 2019 [Zimmerman, Microfluidics: History, Theory and Applications, Chapter 11(2006)] at 156; *id.* at (citing Ismagilov et al. as reference (9)).

As another example, the Ismagilov group’s 2003 publication was described in a 2007 publication as “elegant”:

Droplet-based microfluidic systems provide a controlled environment in which to perform rapid mixing, isolation of picoliter-size fluid volumes, and rapid variation of reaction conditions. *An elegant example of this facility has been demonstrated by Ismagilov and colleagues, in which they used droplets to measure reaction kinetics on the millisecond time scale.*

Ex. 2020 [Srisa-Art et al., Anal. Chem., 2007] at 6682.

Such praise extends to specific developments that have unlocked microfluidic droplets as systems for studying autocatalytic biological reactions. The '193 patent explicitly claims “conditions suitable for the autocatalytic reaction in the at least one plug...” '193 patent at claim 1. As documented above, due to the high surface-to-volume environment of a droplet, it is not a trivial matter to create such conditions in a droplet. *See supra* 43-44. This claim requirement is taught nowhere in the cited art. *See supra* Part IV.C.1. Prior to Ismagilov, there was a long felt need for a way to create such conditions. In 2005, Ismagilov and co-workers' published one such solution, which was based on the use of specific fluorinated surfactants including a hydrophilic oligoethylene glycol head group (R_f -OEG surfactants) to provide an inert, biocompatible interface:

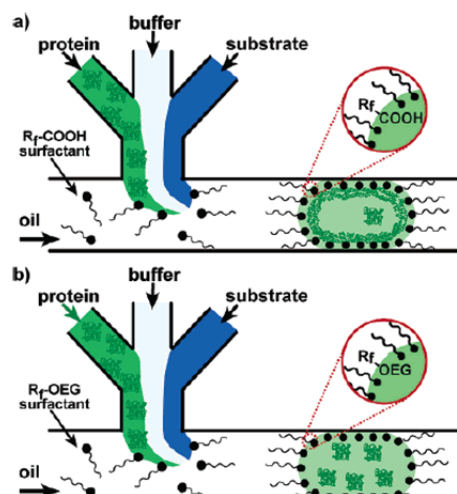


Figure 1. Controlling surface chemistry in plug-based microfluidic devices with surfactants at the aqueous-fluorous interface. (a, b) Schematic of surfactant molecules at the interface of an aqueous plug of protein in a microfluidic channel. (a) R_f -COOH surfactant provided a noninert interface prone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

Ex. 2021 [Roach et al., Anal Chem. 2005] at 789. Notably, the oligoethylene-

terminated surfactants identified by Petitioner's expert are the molecules invented by Ismagilov's group and described in the Ismagilov Patents. *See* '193 patent at 36:38-59. Researchers have widely praised the solution of Ismagilov's team.

For instance, the Petitioner's expert acknowledged the importance of the surface chemistry problems in droplets, further citing the 2005 paper the Ismagilov group and co-workers as providing a solution:

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. 2013 [Theberge et al., *Angew. Chem.* 2010] at 5852 (citing L. S. Roach, H. Song, R. F. Ismagilov, *Anal. Chem.* 2005, 77, 785).

Similarly, a 2009 article described this contribution as "major work":

Ismagilov et al. did major work concerning droplet micro-fluidics¹⁹ and concerning the chemistry of the surfactants and oils used to perform the above experiments.⁶¹ 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.

Ex. 2022 [Leng et al., Lab on a Chip 2009] at 29 (reference 61 is L. S. Roach, H. Song, R. F. Ismagilov, Anal. Chem. 2005, 77, 785). If, as Petitioner contends, it were obvious to create conditions suitable for doing PCR in droplets, researchers in the field would never have characterized it as “major work.”

Likewise, a 2006 article described the issue of protein adsorption as an “important consideration,” citing the Ismagilov group’s solution to this problem based on the use of a fluorinated surfactant:

An important consideration in performing such studies is protein adsorption into the microfluidic device surface, however the same group developed methods of altering droplet interfacial chemistry to actively prevent such problems.⁶³ These developments can be further extended for the creation of artificial membranes on the droplet surface.

Ex. 2023 [Breslauer et al. Mol. Bio Systems 2006] at 106 (reference 63 is L. S. Roach, H. Song, R. F. Ismagilov, Anal. Chem. 2005, 77, 785).

As yet another example, a 2008 article described the importance of the surfactant formulation to droplet stability and its “crucial” role in preventing harmful protein-surface interactions. The article cited the Ismagilov group’s solution to the problem, noting the publication’s demonstration “that with proper choice of surfactant it is possible to decrease the likelihood of protein localization at the interface of the droplet and allow uniform distribution throughout the whole

droplet.” Ex. 2011 [Huebner et al., Lab on a Chip 2008] at 1248 (passage further citing L. S. Roach, H. Song, R. F. Ismagilov, Anal. Chem. 2005, 77, 785).

As recently as 2013, researchers described the “crucial” need to avoid protein adsorption at the droplet/carrier-fluid interface, and pointed to two publications by Ismagilov and colleagues documenting their synthesis of a “new surfactant” that solved the problem:

Fluorescence imaging has outstanding advantages in studying the spatial distribution of interested molecules in droplets and surrounding phase. The control of protein adsorption on the interface between droplet and carrier phase is crucial in enzyme kinetics study and biochemical assay. Roach et al. [59] studied the protein adsorption on droplet–oil interface with fluorescently labeled proteins and confocal fluorescence microscopy (Fig. 3C). Their study indicated the nonspecific protein adsorption could be prevented by using oligoethylene-glycol capped surfactants in carrier phase. In the subsequent study, they designed a new surfactant to induce specific adsorption of proteins at the interface and used it to improve the success rate of protein crystallization [60]

Ex. 2024 [Zhu and Fang, Analytica Chimica Acta 2013] at 28 (reference 59 is L. S. Roach, H. Song, R. F. Ismagilov, Anal. Chem. 2005, 77, 785).

2. Failure Of Others

The Petition contends that the claimed invention would have been obvious in

view of Quake and Haff. It is particularly compelling evidence of non-obviousness, then, that the named inventors on the Quake reference, Todd Thorsen and Stephen Quake, were unsuccessful in their 2003 attempts to conduct a model enzymatic assay in droplets using their microfluidic “crossflow” system.

Thorsen’s 2003 dissertation documents their efforts to assay *E. coli*. P-nitrobenzyl esterase activity in bacterial cells captured in microfluidic droplets. *See* Ex. 2008 [Thorsen Dissertation 2003] at 94-108. As Thorsen explains, the “crossflow assay was unreliable,” *id.* at 100, and resulted in “hundreds” of failed efforts “ultimately discarded in an attempt to discover the perfect operating conditions.” *Id.* at 101-02. 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.

Notably, the areas of future research identified by Thorsen—adhesion of

cells to channel walls and reagent stability—are the *wrong* issues. The insight provided by the Ismagilov team was that one needed to focus on the droplet surface, not, as Thorsen suggested, the channel surface. Likewise, droplet microfluidics did not require improvements in reagent stability, but improvements in the environment for the reagent. The Ismagilov team invented a new system to stabilize droplets in a way that kept enzymes functional without making any changes to the reagents (enzymes or substrates) to make them more stable. As documented herein, the Haff and Quake references fall far short of rendering the claimed inventions of the Ismagilov Patents obvious. Thorsen’s doctoral thesis would have just led the skilled artisan further astray because it would have directed such a person to work on the wrong problems. The fact that the named inventor on the reference that allegedly renders the claimed inventions obvious was pointing in the wrong direction is strong evidence of non-obviousness.

V. CONCLUSION

Patent Owner respectfully submits that the Petition should be dismissed and/or denied for at least the foregoing reasons. Because this is only Patent Owner’s Preliminary Response, it is not a comprehensive rebuttal to all arguments raised in the Petition. Patent Owner reserves the right to contest the Petition on all grounds permitted. Nothing herein should be construed as a concession or admission by Patent Owner as to any fact or argument in the Petition.

Respectfully submitted,

WEIL, GOTSHAL & MANGES, LLP

Dated: August 17, 2015

/Adrian Percer/

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **THE UNIVERSITY OF CHICAGO'S PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,304,193 PURSUANT TO 37 CFR § 42.107** is being served on August 17, 2015, via email pursuant to 37 C.F.R. § 42.6(e) to counsel for 10X Genomics, Inc., at the addresses below:

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