

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.

Petitioner

v.

THE UNIVERSITY OF CHICAGO

Patent Owner

U.S. Patent No. 8,304,193 to Ismagilov *et al.*

Issue Date: November 6, 2012

Title: Method of Conducting an Autocatalytic
Reaction in Plugs in a Microfluidic System

Inter Partes Review No. Unassigned

**Petition For *Inter Partes* Review of U.S. Patent No. 8,304,193 Under 35 U.S.C.
§§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123**

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I. Introduction

10X Genomics, Inc.'s ("Petitioner") Petition for *Inter Partes* Review ("Petition") seeks cancellation of claim 1-9 and 11 of U.S. Patent No. 8,304,193 ("the '193 patent") (GEN1001) as unpatentable under 35 U.S.C. § 103(a) in view of the prior art.

The '193 patent claims are directed to methods of performing an autocatalytic reaction, such as the polymerase chain reaction ("PCR"), in volumes of an aqueous fluid that are encapsulated by an immiscible carrier fluid, and are flowing through a microfluidic system. However, by May 2002¹, all of the elements of the '193 patent claims were present in the prior art.

For instance, performing autocatalytic reactions, such as PCR, in microfluidic systems was well-known by May 2002. Indeed, the Petitioner's primary reference, Haff, demonstrates as much. Likewise, generating plugs of an aqueous fluid encapsulated by an immiscible carrier fluid was nothing new in the art by May 2002, as evidenced by the Quake reference discussed in this Petition. And this Petition demonstrates that a person of ordinary skill in the art ("POSA") would have had a reason to modify Haff in view of Quake to overcome the loss of

¹ Petitioner does not concede that the '193 patent is entitled to a filing date of May 9, 2002. Regardless, however, the '193 patent cannot be entitled to any filing date earlier than May 9, 2002.

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reagents that occurs in systems like Haff's. Indeed, the '193 patent claims are no more than a combination of these prior art elements disclosed in Haff and Quake that yields predictable results. As such, it would have required no more than routine skill and knowledge in the art for a POSA to successfully arrive at the claims of the '193 patent in view of these references. And no objective indicia of nonobviousness weighs in favor of patentability. Consequently, the claims of the '193 patent would have been obvious and should be cancelled.

II. Grounds for standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '193 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR of any of the challenged claims.

III. Statement of the precise relief requested and the reasons therefor

Petitioner requests that the Office institute IPR and cancel claims 1-9 and 11 of the '193 patent as unpatentable under 35 U.S.C. § 103(a). Petitioner's full statement of the reasons for the relief requested is set forth in detail in § VI.

IV. Overview

A. Person of ordinary skill in the art ("POSA") and state of the art

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA in the field of microfluidic devices and the methods of using such devices would have had knowledge of the scientific literature concerning microfluidic devices and the methods of using such devices before May

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9, 2002. (GEN1002, ¶14.) A POSA would have had knowledge of strategies for performing chemical and biological analysis in microfluidic devices. (*Id.*) Typically, a POSA would have had a Ph.D. in chemistry, biochemistry, mechanical engineering, or a related discipline, with two years of experience in using, designing or creating microfluidic devices. (*Id.*) Alternately, a POSA could have had a M.S. or bachelor's degree in one of these disciplines with four or five years of additional relevant experience, respectively. (*Id.*) A POSA would have known how to research the scientific literature in fields relating to microfluidics, including fluid dynamics, microscale reactions, chemistry, biochemistry, and mechanical engineering. (*Id.*) Also, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others in the team, *e.g.*, to solve a given problem. (*Id.*) For example, a chemist, engineer, and a biologist may have been part of the team. (*Id.*)

Before May 9, 2002, the state of the art included the teachings provided by the references discussed in this Petition. Additionally, a POSA would have been aware of other important references relating to performing reactions, including PCR, in microfluidic devices.

1. Analyzing biological samples and performing chemical reactions in microfluidic devices were well-known in the art by May 2002

Since at least 1957, capillary systems for analyzing biological samples, such as blood and urine, were well-known in the art. (GEN1008, 1:15-19², 2:62-70, Fig. 3; GEN1002, ¶16.) In these systems, a biological sample was introduced into a main capillary channel. (GEN1008, 4:6-18; GEN1002, ¶16.) Pockets of air were injected into the channel in an alternating fashion with each biological sample. (GEN1008, 4:29-34; GEN1002, ¶16.) This injection method resulted in a segmented stream composed of alternating segments of air and biological sample, *i.e.*, slugs of air and biological sample. (GEN1008, 4:37-42; GEN1002, ¶16.) Similar systems were also developed that injected an immiscible fluid, such as mineral oil, instead of air to create the segmented stream—resulting in alternating slugs of immiscible fluid and biological sample. (GEN1009, 3:11-37; GEN1002, ¶16.)

However, these systems had drawbacks. For instance, it was well-known

² Citations to patent literature provided as GEN10XX, YYY:Z-Z indicate citations to column Y, at lines Z-Z. For example, GEN10XX, 1:1-10 indicates column 1, lines 1-10. Citations to non-patent literature provided as GEN10XX, Y:Z indicate citations to page number Y, at column number Z. For example, GEN10XX, 10:1 indicates p. 10, at column 1.

that the contents of slugs containing biological samples or chemical reactants could adhere to channel walls and contaminate the next successive slug. (GEN1008, 4:42-54; GEN1010, 1:57-59; GEN1002, ¶17.) And while the intervening air or immiscible fluid could minimize this cross-contamination, it did not completely cure the problem. (GEN1010, 1:68-2:4; GEN1002, ¶17.)

To solve this problem of cross-contamination, Smythe *et al.* developed a fluid analysis system, in which a sample fluid was aspirated into a channel made of fluorinated hydrocarbon. (GEN1010, 1:68-2:4, 2:35-61; GEN1002, ¶18.) In Smythe's system, a silicone fluid flowing within the fluorinated hydrocarbon channel wets the channel walls and forms a film that adheres to the channel walls. (GEN1010, 2:35-61 and Fig. 1; GEN1002, ¶18.) This method prevented the loss of material from the volumes of sample fluid, and thus cross-contamination. (GEN1010, 2:50-58; GEN1002, ¶18.) This is because "[t]he aqueous sample segments do not touch this inner wall of the conduit, but, ... rather, travel within the film of silicone." Further, "[t]he aqueous sample segments do not adhere to the silicone film and thus do not leave a deposit of sample thereon, to contaminate successive sample segments." (GEN1010, 2:53-58; GEN1002, ¶18.) Thus, Smythe's method resulted in a volume of sample fluid encapsulated by a thin film of silicone fluid, which would travel within the film of silicone fluid and not touch or adhere to the inner walls of the fluorinated hydrocarbon channel. (GEN1010,

2:35-61, Fig. 1; GEN1002, ¶18.) However, this system also required injecting encapsulated volumes of air or an inert gas between the encapsulated volumes of sample fluid to prevent coalescence of the encapsulated volumes of sample fluid. (GEN1010, 2:62-71; GEN1002, ¶18.)

In 1984, Shaw Stewart developed a microfluidic system for performing chemical reactions. (GEN1011, Abstract; GEN1002, ¶19.) Shaw Stewart explicitly stated that an object of his system was “to reduce or eliminate contamination of the reactants[.]” (GEN1011, p. 2; GEN1002, ¶19.) To achieve this goal, Shaw Stewart’s system injected an aqueous fluid containing a chemical reactant through one inlet into a main channel in which a carrier fluid, such as a fluorinated oil, was flowing. (GEN1011, Abstract, pp. 3-4; GEN1002, ¶19.) As a result of this process, volumes of the aqueous fluid were sheared off into droplets that were encapsulated by the carrier fluid present in the main channel. (GEN1011, pp. 3-4; GEN1002, ¶19.) This process was repeated to inject a second chemical reactant through a second channel. (GEN1011, pp. 3-4; GEN1002, ¶19.) The droplets containing the first reactant and the second reactant were then coalesced to combine the reactants. (GEN1011, pp. 3-4; GEN1002, ¶19.)

2. PCR and its performance in microfluidic devices were well-known in the art by May 2002

Developed in 1985, PCR revolutionized the field of molecular biology by allowing researchers to selectively amplify a DNA sequence of interest.

(GEN1029, 230:3-231:1; GEN1002, ¶20.) And since its introduction, PCR has become a fundamental technique in biotechnology labs, allowing for the amplification of target DNA sequences for use in techniques such as DNA sequencing and molecular cloning. (GEN1016, 138:1; GEN1002, ¶20.) By 1987, the first thermocycler machine, which automated the performance of PCR, was commercially available. (GEN1030, 2727:1; GEN1021, 1:50-58; GEN1002, ¶21.) A drawback to thermocyclers, however, was that they required reaction volumes in the range of 10µl-50µl for efficient production of PCR products. (GEN1033, 484:1; GEN1002, ¶21.) Such volumes can be problematic when conservation of reagents—such as template DNA, primers, or polymerase—is necessary. (GEN1033, 484:1; GEN1015, 271:1; GEN1002, ¶21.)

Therefore, beginning in the 1990's, researchers began to develop microfluidic devices that could perform PCR on a nanoliter scale. In 1993, Northrup *et al.* developed the first “miniaturized thermal cycling device for application to the polymerase chain reaction (PCR).” (GEN1014, Abstract; GEN1002, ¶22.) In the following years, others developed similar devices “for isothermal amplification of nucleic acids in ... microfabricated substrate[s],” including “integrated DNA analysis system[s] comprised of microfluidic valves and vents, PCR amplification chambers, and capillary electrophoretic separation channels.” (GEN1016, Abstract; *see also* GEN1012, Abstract; GEN1015, Abstract;

GEN1017, Abstract; GEN1032, pp. 89-104; GEN1034, ¶¶[0050]-[0086]; GEN1035, 11:1-61 and Fig. 4; GEN1002, ¶22.) And “the stochastic PCR amplification and analysis of single-molecule DNA templates using an integrated glass microdevice” was developed. (GEN1031, Abstract, 570:2, ¶2; GEN1002, ¶22.) Each of these systems functioned by injecting a stream of a single PCR reaction mixture into the device, which was then flowed into a microfluidic PCR reaction chamber, where the target sequence was amplified via thermocycling. (GEN1002, ¶22.)

Advantages of these systems included, *inter alia*, a need for less reagent and a reduction in time necessary to amplify a target sequence. (GEN1016, 138:2; GEN1015, 277:2-278:1, 280:2; GEN1002, ¶23.) But there were also disadvantages. For instance, because a single stream of PCR reaction mixture was injected into the device, only a single DNA sample could be analyzed per channel. (GEN1002, ¶23.) Additionally, target DNA and reagents could diffuse throughout the stream and out of PCR reaction zones, causing uneven, or even lack of, exposure to thermal incubations. (*See, e.g.*, GEN1032, p. 104; GEN1002, ¶23.)

Later-developed microfluidic PCR devices addressed the problems of reagent diffusion and precise control of thermocycling by injecting slugs of aqueous PCR reaction mixtures separated by air or by a fluid with which the PCR reaction mixture was immiscible, reproducing the methods used in the systems

described above in § IV.A.1. (GEN1021, 10:20-37; GEN1013, ¶¶[0095]-[0116]; GEN1002, ¶24.) However, like in the earlier-developed systems described above, slug adherence and cross-contamination were still an issue. (GEN1002, ¶24.)

Building upon the microfluidic systems described above, in 2000, Quake *et al.* developed a system similar to that of Shaw Stewart. (GEN1004; *see* GEN1005; GEN1002, ¶25.) Quake's system, like Shaw Stewart's, sheared off an aqueous fluid—flowing through an inlet and into a main channel—into “droplets” encapsulated by an immiscible fluid. (GEN1004, ¶¶[0015], [0125], [0290], [0287]; *see* GEN1005, 6:17-19, 38:16-19; 82:23-83:4, 82:2-3; 86:21-24; GEN1002, ¶25.) Quake's “droplets” can conform to the size and shape of the channel, while maintaining their respective volumes. (GEN1004, ¶¶[0091]-[0092]; *see* GEN1005, 27:22-28:6; GEN1002, ¶25.) Consequently, Quake's “droplets” were separated from the channel wall by a thin film of the immiscible fluid. (GEN1002, ¶25.) And as such, Quake's “droplets” are the same as the “plugs” recited in the '193 patent claims. (*See* § V, below; GEN1002, ¶25.)

Quake's system allowed for the continuous production of encapsulated droplets at a fixed frequency. (GEN1004, ¶[0290]; *see* GEN1005, 82:23-83:4; GEN1002, ¶25.) Moreover, according to Quake, his system prevented cross-contamination between the encapsulated droplets of aqueous fluid because “there is no problem with the material diffusing or exchanging positions.” (GEN1004,

¶[0014]; *see* GEN1005, 6:12-13; GEN1002, ¶25.)

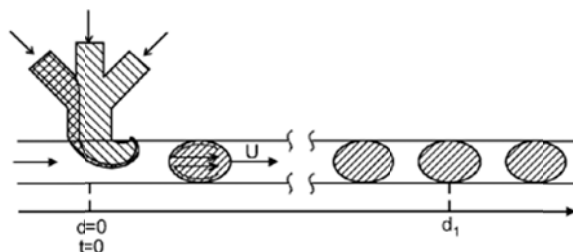
Further, Quake stated that his system could be used to perform PCR—which as discussed above had already been performed in microfluidic devices. (GEN1004, ¶[0080]; *see* GEN1005, 24:12-13; GEN1002, ¶26.) Moreover, Quake disclosed that an advantage of his system is the capability to generate plugs containing single particles, such as polynucleotides. (GEN1004, ¶[0015]; *see* GEN1005, 6:27-7:3; GEN1002, ¶26.)

B. The '193 patent

Against this backdrop, Ismagilov *et al.* filed the patent application that issued as the '193 patent. (GEN1001.) The '193 patent claims priority to May 9, 2002, and is assigned to the University of Chicago (“Patent Owner”), according to the Office’s electronic-assignment records.

The '193 patent claims methods of performing an autocatalytic reaction in plugs of an aqueous fluid flowing in a carrier-fluid in a microfluidic device. (GEN1001, 78:8-63; GEN1002, ¶30.) The methods claimed in the '193 patent recite flowing an aqueous fluid through a first channel into a main channel in which a flowing oil is present. (GEN1001, 78:12-17; GEN1002, ¶30.) The aqueous fluid comprises a substrate molecule and reagents for conducting the autocatalytic reaction. (GEN1001, 78:18-26; GEN1002, ¶31.) And upon introduction of the aqueous fluid from the first inlet into the main channel, the oil partitions the

aqueous fluid into a plug that is substantially surrounded by the oil and that then flows through the main channel. (GEN1001, 78:18-26; GEN1002, ¶30.) Figure 2A-2 of the '193 patent, reproduced below, is illustrative of this process:



(GEN1001, Fig. 2A-2; GEN1002, ¶30.) The claims then require providing conditions suitable for conducting the autocatalytic reaction in the plug to amplify the substrate molecule. (GEN1001, 78:27-29; GEN1002, ¶31.)

V. Claim construction

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretations in light of the specification of the '193 patent. Terms not explicitly discussed below are plain on their face and should be construed to have their ordinary and customary meanings.

Plug of the aqueous fluid: Claim 1 requires, *inter alia*, forming at least one “plug of the aqueous fluid.” (GEN1001, 78:18.) The '193 patent defines plugs as follows:

“Plugs” 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. The flow of the fluids in the device is induced by a driving force or

stimulus that arises, directly or indirectly, from the presence or application of, for example, pressure, radiation, heat, vibration, sound waves, an electric field, or a magnetic field. Plugs in accordance with the present invention may vary in size but when formed, their cross-section should be substantially similar to the cross-section of the channels in which they are formed. When plugs merge or get trapped inside plug traps, the cross-section of the plugs may change. For example, when a plug enters a wider channel, its cross-section typically increases.

(*Id.*, 9:27-40.) The specification further defines the term “plug-fluid” as “a fluid wherein or using which a reaction or precipitation can occur,” and the term “carrier-fluid” as “a fluid that is immiscible with a plug-fluid.” (*Id.*, 10:1-2 and 7:42-43.) Additionally, the specification further describes the relationship between the carrier-fluid and plug fluid, stating:

The carrier-fluid preferably wets the walls of the channels preferentially over the plugs. If this condition is satisfied, the plug typically does not come in contact with the walls of the channels, and instead remains separated from the walls by a thin layer of the carrier-fluid. Under this condition, the plugs remain stable and do not leave behind any residue as they are transported through the channels.

(GEN1001, 20:59-65; GEN1002, ¶34.)

The '193 patent states that the plugs “may be in the form of plugs comprising an aqueous plug-fluid containing one or more reagents and/or one or more products formed from a reaction of the reagents, wherein the aqueous plug-

fluid is surrounded by a non-polar or hydrophobic fluid such as an oil.” (GEN1001, 9:45-50.)

As such, a POSA would have understood the broadest reasonable interpretation of “plugs of the aqueous fluid” to be “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.” (GEN1002, ¶36.)

Autocatalytic reaction: Claim 1 recites “a method for conducting an autocatalytic reaction in plugs.” (GEN1001, 78:8-9.) The ’193 patent does not define the term “autocatalytic reaction.” (GEN1002, ¶37.) But claim 3, which depends from claim 1, specifies that “the autocatalytic reaction is a polymerase-chain reaction [(“PCR”).]” (GEN1001, 78:32-34.) As such, the broadest reasonable interpretation of “autocatalytic reaction” encompasses at least PCR.

Conditions suitable for the autocatalytic reaction ... such that the at least one substrate molecule is amplified: Claim 1 requires, *inter alia*, “providing conditions suitable for the autocatalytic reaction in the at least one plug ... such that the at least one substrate molecule is amplified.” (*Id.*, 78:27-29.) The ’193 patent does not define the term autocatalytic reaction, or describe specific

conditions for amplifying the at least one substrate molecule. (GEN1002, ¶38.) But the '193 patent discloses that “[a] reagent contained in a plug-fluid may undergo a reaction in which a stimulus such as radiation, heat, temperature or pressure change, ultrasonic wave, or a catalyst induces a reaction to give rise to the transformation of the reagent to another reagent, intermediate, or product.” (GEN1001, 11:4-9.) Therefore, the broadest reasonable interpretation of “conditions suitable for the autocatalytic reaction in the at least one plug ... such that the at least one substrate molecule is amplified” 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. (GEN1002, ¶¶38-39.)

Substantially surrounded: Claim 1 requires, *inter alia*, that the plugs of the aqueous fluid are “substantially surrounded by an oil.” (GEN1001, 78:21-22.) As discussed above, in defining “plugs,” the '193 patent describes the interface between the aqueous plugs and the immiscible carrier fluid in terms of the plugs being “surrounded” by the carrier fluid: “wherein the aqueous plug-fluid is surrounded by a non-polar or hydrophobic fluid such as an oil.” (*Id.*, 9:48-50 (emphasis added).) But the '193 patent also describes this same fluid interface in terms of the plugs being “encapsulated” by the carrier fluid:

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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. First, the substantial dispersion of solutes in microfluidic channels increases reagent consumption and makes experiments or measurements over long time scales (e.g., minutes to hours) difficult to perform. Various devices and methods according to the invention are intended to overcome this problem by localizing reagents inside plugs that are encapsulated by an immiscible carrier-fluid.

(*Id.*, 11:54-63 (emphasis added).)

Because the '193 patent uses the terms “surrounded” and “encapsulated” interchangeably when describing the fluid interface between the aqueous plugs and the immiscible carrier fluid, the broadest reasonable interpretation of “surrounded” includes “encapsulated.” *See Solvay S.A. v. Honeywell Int’l, Inc.*, 622 F.3d 1367, 1380 (Fed. Cir. 2010) (holding that the claim term “isolating” can properly be construed to mean “separating” when the word “isolate” is used interchangeably with the word “separate” in the specification describing a chemical process); (GEN1002, ¶42).

Although the '193 patent contains no express disclosure for the term “substantially surrounded” or encapsulated in this context, it teaches that the invention is intended to overcome the problem of “dispersion of solutes in microfluidic channels [which] increases reagent consumption and makes

experiments or measurements over long time scales (e.g., minutes to hours) difficult to perform.” (GEN1001, 11:57-60; GEN1002, ¶42.) The ’193 patent overcomes this problem “by localizing reagents inside plugs that *are encapsulated by an immiscible carrier-fluid.*” (GEN1001, 11:62-63 (emphasis added); GEN1002, ¶42.) Thus, given that plugs have a cross-section that is substantially similar to the cross-section of the channels in which they are formed, a POSA would have understood that the broadest reasonable interpretation of “substantially surrounded” encompasses plugs that are “entirely” surrounded or encapsulated by a thin layer of the immiscible carrier fluid existing between the plugs and the channel walls. (GEN1002, ¶42.) This would result in preventing the problem of solute dispersion out of plugs. (*Id.*, ¶42.)

Claim 1’s preamble is limiting: Claim 1’s preamble recites “[a] method for conducting an autocatalytic reaction in plugs in a microfluidic system.” (GEN1001, 78:8-9.) “When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.” *Eaton Corp. v. Rockwell Int’l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003). Here, the limitation of “the microfluidic system” (GEN1001, 78:10) in the body of claim 1 derives its antecedent basis from the preamble of claim 1. Moreover, a POSA reading the plain language of claim 1 would understand that it requires that the autocatalytic

reaction is performed within the plugs while they are in the microfluidic system. (GEN1002, ¶43.) So, under the broadest reasonable interpretation, claim 1 requires that the autocatalytic reaction is conducted within the plugs while they are in the microfluidic system.

Carrier fluid: Claim 7 depends from claim 1 and requires that “the carrier fluid further comprises a surfactant.” (GEN1001, 78:42-43.) The term “carrier fluid” has no antecedent basis in claim 1. However, a POSA would have understood that the “carrier fluid” of claim 7 is “the oil” of claim 1. (GEN1002, ¶45.) This is because the ’193 specification discloses using an oil as a carrier fluid: “Suitable carrier-fluids include oils, preferably fluorinated oils.” (GEN1001, 20:23-24; GEN1002, ¶45.)

Merged plug: Claim 9 depends from claim 1 and requires that “the at least one plug is a merged plug.” (GEN1001, 78:46-47.) The ’193 patent discloses:

The invention also provides a method of merging of plugs within a substrate (see upper portion of FIG. 12) ... Plugs containing different reagents can be formed by separately introducing different plug-fluids into a channel. The plugs containing different reagents may be substantially similar in viscosity or may differ. The plugs containing different reagents may be substantially similar in size or they may differ in size. Provided that the relative velocities of the plugs containing different reagents differ, the plugs will merge in the channels. The location of merging can be controlled in a variety of

ways, for example by varying the location of plug-fluid inlet ports, by varying the location of channel junctions (if one of the plug forming fluids is introduced into a secondary channel), varying the size of the plugs, adjusting the speed at which different sets of plugs are transported[,], varying the viscosity or surface tension of plugs having substantially the same size, etc.

(*Id.*, 27:7-24.) As such, a POSA would understand that a merged plug is a plug formed by combining two plugs. (GEN1002, ¶44.) A POSA would further understand that plugs containing different reagents can be formed in a channel by separately introducing different plug-fluids into the channel. (*Id.*) Thus, a POSA would understand that the broadest reasonable interpretation of forming merged plugs encompasses combining two plugs by, for example, varying the relative velocity of the different plugs relative to each other and at least by varying the location of plug-fluid inlet ports. (*Id.*)

Substantially spherical in shape: Claim 11 depends from claim 1 and recites that “the at least one plugs is substantially spherical in shape.” (GEN1001, 78:51-52.) The ’193 patent states that “plugs in accordance with the present invention may vary in shape, and for example may be spherical or non-spherical [, and that the] shape of the plug may be independent of the shape of the channel (e.g., a plug may be a deformed sphere traveling in a rectangular channel).” (*Id.*, 9:41-45.) And the ’193 patent further discloses:

For applications involving visualization of mixing, the substrate is

designed to include a narrow channel in the plug-forming region is designed [sic] such that narrow, elongated plugs form. Immediately downstream from the plug-forming region, the channel dimension is preferably expanded. In the expanded region of the channel(s), plugs will expand and become short and rounded under the force of surface tension.

(*Id.*, 25:39-45.)

As such, a POSA would understand that the force of surface tension between the aqueous plug and oil substantially surrounding the plug would cause a plug to assume a spherical shape in an expanded channel, unless the shape of the channel deforms the plug. (GEN1002, ¶46.) For example, even in a rectangular expanded channel, the plug does not assume a rectangular shape—rather, it becomes a deformed sphere. (GEN1001, 9:41-45; GEN1002, ¶46.) Thus, a POSA would understand that a plug assumes a substantially spherical shape in a round expanded channel, because the round channel would not deform the plug. (GEN1002, ¶46.) As such, a POSA would understand that a plug that is “substantially spherical in shape” encompasses a plug present in a round expanded channel. (*Id.*, ¶47.)

VI. Identification of challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of claims 1-9 and 11 of the '193 patent. Per 37 C.F.R. § 42.6(c), copies of the references accompany the Petition. The Grounds for unpatentability are further supported by the accompanying declaration of Dr. Huck, Ph.D. (“Huck Dec.”) (GEN1002), an expert in the fields of microfluidics

and microscale reactions.

Ground	35 U.S.C. Section (pre-3/16/2013)	Claims	Index of References
1	§ 103(a)	1-5, 7-9, and 11	Haff and Quake
2	§ 103(a)	6	Haff, Quake, and Ramsey

A. Ground 1: Claims 1-5, 7-9, and 11 would have been obvious over Haff in view of Quake

As supported by the declaration of Dr. Huck, claims 1-5, 7-9, and 11 would have been obvious over U.S. Patent No. 6,033,880 (“Haff”) (GEN1021) in view of U.S. Patent App. Pub. No. US 2002/0058332 (“Quake”) (GEN1004). (GEN1002, ¶¶53-112.) Haff qualifies as prior art to the ’193 patent claims under 35 U.S.C. § 102(b) because it issued on March 7, 2000.

Quake qualifies as prior art under 35 U.S.C. § 102(e) as of September 14, 2001 and as of September 15, 2000. First, Quake was filed by another on September 14, 2001, and published on May 16, 2002. Thus, Quake qualifies as prior art under 35 U.S.C. § 102(e) to the ’193 patent claims as of its September 14, 2001 filing date.

Second, Quake claims priority to U.S. Prov. Appl. No. 60/233,037 (“the ’037 application”) (GEN1005), filed on September 15, 2000. The disclosures relied upon in Quake that teach the ’193 patent claim limitations are also found in the ’037 application and carry over into Quake. (GEN1002, ¶53). Indeed, throughout

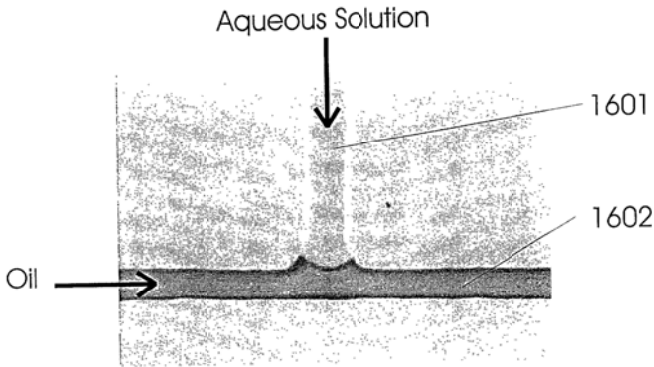
this petition, Petitioner cites to both Quake and the '037 application to show where the '193 patent claim limitations are found in both. This evidences that the disclosures of Quake relied upon to demonstrate unpatentability of the '193 patent claims are fully supported in the '037 application. Thus, Quake also qualifies as prior art under 35 U.S.C. § 102(e) to the '193 patent claims as of the '037 application's filing date of September 15, 2000. *See In re Giacomini*, 612 F.3d 1380 (Fed. Cir. 2010); *see also Ex parte Yamaguchi*, 88 USPQ2d 1606 (BPAI 2008).

Claim 1 would have been obvious over the combination of Haff and Quake, as shown below.

Claim 1	Haff (GEN1021) in view of Quake (GEN1004)³
A method for conducting an autocatalytic reaction in plugs in a microfluidic system, comprising the steps of:	<p style="text-align: center;"><u>Haff</u></p> <p>“This invention relates to amplifying nucleic acids by thermal cycling and, more particularly, to automated machines for performing amplification reactions such as a polymerase chain reaction (PCR).” (GEN1021, 1:12-15.)</p> <p style="text-align: center;"><u>Quake</u></p> <p>“A microfluidic device for analyzing and/or sorting biological materials (e.g., molecules such as polynucleotides and polypeptides ...) ... The microfluidic device comprises a main channel and an inlet region in communication with the main channel at a droplet extrusion region. Droplets of solution containing the biological material are deposited into the main channel</p>

³ Emphasis added unless otherwise indicated.

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
	<p>through the droplet extrusion region.” (GEN1004, [Abstract]; <i>see</i> GEN1005, Abstract.)</p> <p>“The sample fluid is, specifically, a fluid which is incompatible with the extrusion fluid and contains the biological material or sample. Thus, droplets of the sample fluid containing the biological material for analysis, reaction or sorting are sheared at the droplet extrusion region into the flow of the extrusion fluid in the main channel.” (GEN1004, ¶[0020]; <i>see</i> GEN1005, 8:16-20.)</p> <p>“Microfabrication permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR” (GEN1004, ¶[0080]; <i>see</i> GEN1005, 24:12-13.)</p>
<p>providing the microfluidic system comprising at least two channels having at least one junction;</p>	<p style="text-align: center;"><u>Quake</u></p> <p>“A microfluidic device provided by the invention comprises a main channel and at least one inlet region which is in communication with the main channel at a droplet extrusion region.” (GEN1004, ¶[0015]; <i>see</i> GEN1005, 7:6-10.)</p> <p>“The devices and methods of the invention comprise a main channel, through which a pressurized stream of oil is passed, and at least one sample inlet channel, through which a pressurized stream of aqueous solution is passed. A junction or ‘droplet extrusion region’ joins the sample inlet channel to the main channel such that the aqueous solution can be introduced to the main channel, e.g., at an angle that is perpendicular to the stream of oil.” (GEN1004, ¶[0003]; <i>see</i> GEN1005, 1:14-19.)</p> <p>“The channel architecture for the droplet extrusion region of the first device is shown in FIG. 16A. In this device, the inlet channel 1601 (inner diameter 30 μm) intersects the main channel 1602 (inner diameter 30 μm) at a T-intersection (i.e., an angle perpendicular to the main channel). Other intersections and angles may be used. The</p>

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
	<p>walls of the inlet and main channels were not tapered in this device. The channel architecture for the second exemplary extrusion region is shown in FIG. 16B. In this device, both the inlet channel 1603 and the outlet channel 1604 have inner diameters of 60 μm. However, the channels 1605 and 1606 taper to inner diameters of 30 μm at the droplet extrusion region.” (GEN1004, ¶[0292]; see GEN1005, 83:8-16.)</p>  <p>FIG. 16A</p> <p>(GEN1004, Fig. 16A; see GEN1005, Fig. 16A.)</p>
<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>	<p>Haff</p> <p>“In the second embodiment of FIG. 2, the motive force for moving the PCR reaction mixture along the tubing 50 is a sterile, disposable syringe 51 capable of holding large volumes of reaction mixture 53. The syringe 51 is loaded with the reaction mixture components well known to those skilled in the art, and the sample nucleic acid to be amplified. The syringe 51 is then operated by hand, compressed gas, or using a syringe pump to move the reaction mixture 53 into and through the tubing 50.” (GEN1021, 10:20-28.)</p> <p>“The reaction mixture is comprised of various components such as the DNA to be amplified (the target) and at least two oligonucleotide primers selected in a predetermined way so as to be complementary to a portion of the target DNA The reaction mixture also</p>

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
	<p>includes various buffers, enzymes, and deoxyribonucleotide triphosphates, such as [d]ATP, dCTP, dGTP, and dTTP.” (<i>Id.</i>, 1:21-27.)</p> <p style="text-align: center;"><u>Quake</u></p> <p>“The devices and methods of the invention comprise a main channel, through which a pressurized stream of oil is passed, and at least one sample inlet channel, through which a pressurized stream of aqueous solution is passed.” (GEN1004¶, ¶[0003]; <i>see</i> GEN1005, 1:14-17.)</p> <p>“Fluid flows continuously through the system and there is no need for charged droplets, so that many difficult technical issues associated with traditional, e. g., FACS devices are avoided.” (GEN1004, ¶[0014]; <i>see</i> GEN1005, 6:3-5.)</p> <p>“[A] first fluid, which may be referred to as an ‘extrusion’ or ‘barrier’ fluid, passes (i.e., flows) through the main channel of the device and a second fluid, referred to as a ‘sample’ or ‘droplet’ fluid, passes or flows through the inlet region. The sample fluid is, specifically, a fluid which is incompatible with the extrusion fluid and contains the biological material or sample.” (GEN1004, ¶[0020]; <i>see</i> GEN1005, 8:14-18.)</p> <p>“Microfabrication permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR” (GEN1004, ¶[0080]; <i>see</i> GEN1005, 24:12-13.)</p>
<p>flowing an oil through the second channel of the at least two channels;</p>	<p style="text-align: center;"><u>Haff</u></p> <p>“Another syringe 55 containing air or an immiscible fluid such as mineral oil may be connected in parallel with the syringe 55 to the tubing 50. The syringe 55 is operated intermittently to inject air bubbles or immiscible fluid bubbles into the flow stream of reagent mixture 53 in the tubing 50.” (GEN1021, 10:29-34.)</p> <p style="text-align: center;"><u>Quake</u></p>

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
	<p>“[A] first fluid, which may be referred to as an ‘extrusion’ or ‘barrier’ fluid, passes (i.e., flows) through the main channel of the device and a second fluid, referred to as a ‘sample’ or ‘droplet’ fluid, passes or flows through the inlet region.” (GEN1004, ¶[0020]; <i>see</i> GEN1005, 8:14-16.)</p> <p>“More specifically, droplets of a solution (preferably an aqueous solution or buffer), containing a sample of molecules, cells or virions, are introduced through a droplet extrusion region into a stream of fluid (preferably a non-polar fluid such as decane or other oil) in the main channel.” (GEN1004, ¶[0113]; <i>see</i> GEN1005, 34:26-29.)</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,</p>	<p style="text-align: center;"><u>Haff</u></p> <p>“The syringe 51 is loaded with the reaction mixture components well known to those skilled in the art, and the sample nucleic acid to be amplified. The syringe 51 is then operated by hand, compressed gas, or using a syringe pump to move the reaction mixture 53 into and through the tubing 50.” (GEN1021, 10:23-28)</p> <p>“The syringe 55 is operated intermittently to inject air bubbles or immiscible fluid bubbles into the flow stream of reagent mixture 53 in the tubing 50. This will ensure that slug flow dominates throughout the flow path[.]” (<i>Id.</i>, 10:31-35.)</p> <p style="text-align: center;"><u>Quake</u></p> <p>“A microfluidic device for analyzing and/or sorting biological materials (e.g., molecules such as polynucleotides and polypeptides ...) ... The microfluidic device comprises a main channel and an inlet region in communication with the main channel at a droplet extrusion region. Droplets of solution containing the biological material are deposited into the main channel through the droplet extrusion region.” (GEN1004, Abstract; <i>see</i> GEN1005, Abstract.)</p>

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
	<p>“A junction or ‘droplet extrusion region’ joins the sample inlet channel to the main channel such that the aqueous solution can be introduced to the main channel, e.g., at an angle that is perpendicular to the stream of oil. By adjusting the pressure of the oil and/or the aqueous solution, a pressure difference can be established between the two channels such that the stream of aqueous solution is sheared off at a regular frequency as it enters the oil stream, thereby forming droplets.” (GEN1004, ¶[0003]; <i>see</i> GEN1005, 1:17-2:2.)</p> <p>“In a preferred embodiment, water droplets are extruded into a flow of oil, but any fluid phase may be used as a droplet phase and any other incompatible or immiscible fluid or phase may be used as a barrier phase.” (GEN1004, ¶[0014]; <i>see</i> GEN1005, 6:14-16.)</p> <p>“Thus, for example, in preferred embodiments wherein droplets of aqueous solution are extruded into a pressurized stream of oil, the pressures of the oil and/or fluid lines are adjusted so that the pressure difference of the oil and water channels at the droplet extrusion region is zero, and the oil and water are in a state of equilibrium. This can be visually observed. Droplet extrusion can then be initiated by slightly adjusting the pressure difference between the different fluids (i.e., at the different inlet lines) so that the droplet fluid (e.g., water) enters the main channel and is sheared off at a fixed frequency. A preferred frequency is 1 Hz because the frequency with which droplets are sheared off into the main channel depends on the pressure difference between the different fluids, the frequency can be readily adjusted by simply adjusting the pressures of the individual fluid lines.” (GEN1004, ¶[0290]; <i>see</i> GEN1005, 82:23-83:4.)</p> <p>“The devices of this invention are useful for partitioning a first fluid into droplets within a second, incompatible fluid.” (GEN1004, ¶[0287]; <i>see</i> GEN1005, 82:2-3.)</p>

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
	<p>“In preferred embodiments, the droplet extrusion region comprises a T-shaped junction between the inlet region and the main channel, so that the second fluid enters the main channel at an angle perpendicular to the flow of the first fluid, and is sheared off into the flow of the first fluid in the main channel.” (GEN1004, ¶[0015]; see GEN1005, 7:7-10.)</p> <div data-bbox="550 577 1196 938" data-label="Image"> </div> <p>FIG. 16A</p> <p>(GEN1004, Fig. 16A; see GEN1005, Fig. 16A.)</p> <p>“For particles (e.g., cells, including virions) or molecules that are in droplets (i.e., deposited by the droplet extrusion region) within the flow of the main channel, the channels of the device are preferably rounded, with a diameter between about 2 and 100 microns, preferably about 60 microns, and more preferably about 30 microns at the crossflow area or droplet extrusion region. This geometry facilitates an orderly flow of droplets in the channels. See e.g. FIG. 16B. Similarly, the volume of the detection region in an analysis device is typically in the range of between about 10 femtoliters (fl) and 5000 fl, preferably about 40 or 50 fl to about 1000 or 2000 fl, most preferably on the order of about 200 fl. In preferred embodiments, the channels of the device, and particularly the channels of the inlet connecting to a droplet extrusion region, are between about 2 and 50 microns, most preferably about 30 microns.</p> <p>In one preferred embodiment, droplets at these dimensions tend to conform to the size and shape of the</p>

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
	<p>channels, while maintaining their respective volumes. Thus, as droplets move from a wider channel to a narrower channel they become longer and thinner, and vice versa....” (GEN1004, ¶¶[00191]-[0092]; <i>see</i> GEN1005, 27:22-28:6.)</p>
<p>the plug being substantially surrounded by an oil flowing through the channel,</p>	<p style="text-align: center;"><u>Quake</u></p> <p>“In embodiments of the invention where an aqueous phase is combined with an oil phase, aqueous droplets are encapsulated or separated from each other by oil.” (GEN1004, ¶[0100]; <i>see</i> GEN1005, 30:2-3)</p> <p>“For particles (e.g., cells, including virions) or molecules that are in droplets (i.e., deposited by the droplet extrusion region) within the flow of the main channel, the channels of the device are preferably rounded, with a diameter between about 2 and 100 microns, preferably about 60 microns, and more preferably about 30 microns at the crossflow area or droplet extrusion region. This geometry facilitates an orderly flow of droplets in the channels. See e.g. FIG. 16B. Similarly, the volume of the detection region in an analysis device is typically in the range of between about 10 femtoliters (fl) and 5000 fl, preferably about 40 or 50 fl to about 1000 or 2000 fl, most preferably on the order of about 200 fl. In preferred embodiments, the channels of the device, and particularly the channels of the inlet connecting to a droplet extrusion region, are between about 2 and 50 microns, most preferably about 30 microns.</p> <p>In one preferred embodiment, droplets at these dimensions tend to conform to the size and shape of the channels, while maintaining their respective volumes. Thus, as droplets move from a wider channel to a narrower channel they become longer and thinner, and vice versa....” (GEN1004, ¶¶[00191]-[0092]; <i>see</i> GEN1005, 27:22-28:6.)</p>
<p>wherein the at least one plug comprises at least one substrate molecule and reagents for conducting an</p>	<p style="text-align: center;"><u>Haff</u></p> <p>“The syringe 51 is loaded with the reaction mixture components well known to those skilled in the art, and the sample nucleic acid to be amplified. The syringe 51 is then operated by hand, compressed gas, or using a syringe pump to move the reaction mixture 53 into and through the tubing 50.” (GEN1021, 10:23-28.)</p>

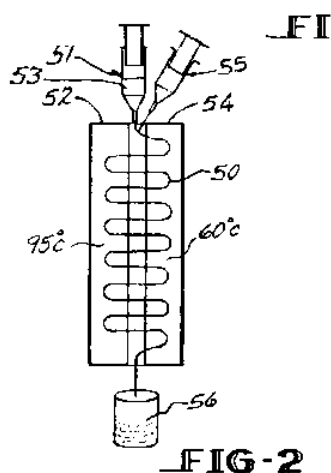
Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
autocatalytic reaction with the at least one substrate molecule; and	<p>“The reaction mixture is comprised of various components such as the DNA to be amplified (the target) and at least two oligonucleotide primers selected in a predetermined way so as to be complementary to a portion of the target DNA The reaction mixture also includes various buffers, enzymes, and deoxyribonucleotide triphosphates, such as [d]ATP, dCTP, dGTP, and dTTP.” (<i>Id.</i>, 1:21-27)</p> <p style="text-align: center;"><u>Quake</u></p> <p>“In preferred embodiments, a first fluid, which may be referred to as an ‘extrusion’ or ‘barrier’ fluid, passes (i.e., flows) through the main channel of the device and a second fluid, referred to as a ‘sample’ or ‘droplet’ fluid, passes or flows through the inlet region. The sample fluid is, specifically, a fluid which is incompatible with the extrusion fluid and contains the biological material or sample. Thus, droplets of the sample fluid containing the biological material for analysis, reaction or sorting are sheared at the droplet extrusion region into the flow of the extrusion fluid in the main channel. Preferably the droplets of the sample fluid each contain, on average, no more than one particle of the biological material.” (GEN1004, ¶[020]; <i>see</i> GEN1005, 8:14-21.)</p> <p>“The concentration (i.e., number) of molecules, cells or virions in a droplet can influence sorting efficiently [sic] and therefore is preferably optimized. 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 to ensure that for the large majority of measurements, the level of reporter measured in each droplet as it passes through the detection region corresponds to a single molecule, cell or virion and not to two or more molecules, cells or virions.” (GEN1004, ¶[0120]; <i>see</i> GEN1005, 37:12-19.)</p>

Claim 1	Haff (GEN1021) in view of Quake (GEN1004) ³
<p>providing conditions suitable for the reaction in the at least one plug involving the at least one biological molecule and the at least one reagent to form a reaction product.</p>	<p style="text-align: center;"><u>Haff</u></p> <p>“This invention relates to amplifying nucleic acids by thermal cycling and, more particularly, to automated machines for performing amplification reactions such as a polymerase chain reaction (PCR).” (GEN1021, 1:12-15)</p> <p>“A simplified schematic diagram of a second embodiment of a capillary tube PCR instrument for performing PCR in comparatively large volumes is shown in FIG. 2. This embodiment uses a length of capillary tubing 50 that is routed in and out of hot and cold sources of the appropriate temperature a number of times. The embodiment of FIG. 2 uses a reaction chamber in the form of series loops of capillary tubing 50. Each loop has a portion which passes through an equilibrated hot zone 52 and a portion which passes through an equilibrated cool zone 54. Typically, the hot zone 52 is a liquid bath wherein the liquid is controlled to have a constant temperature in the range of temperatures needed to perform denaturation in PCR processes, typically around 95° C.” (<i>Id.</i>, 9:55-10:2.)</p> <p>“The length of the tubing 50, its internal diameter, the length of tubing in each of the hot and cool zones, and the flow rate of reaction mixture inside the tube are all factors in the control of the amplification.” (<i>Id.</i>, 10:15-19.)</p> <p>“The preferred method of operation includes leaving an air pocket at the top of the syringe 51 to force all the amplified product out of and completely through the tubing.” (<i>Id.</i>, 10:53-56.)</p> <p style="text-align: center;"><u>Quake</u></p> <p>“Microfabrication permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR” (GEN1004, ¶[0080]; <i>see</i> GEN1005, 24:12-13.)</p>

As supported by the Huck declaration (GEN1002, ¶¶73-74), a POSA would have had a reason to modify the methods disclosed in Haff in view of Quake to arrive at the subject matter of claim 1. This is because Haff's drawbacks of slug adherence to channel walls and resultant loss of reagents due to diffusion are overcome by Quake's method of generating aqueous droplets that are encapsulated, *i.e.*, substantially surrounded, by an oil that forms a thin layer of oil between the droplet and the channel wall to prevent adhesion and diffusion. (*Id.*, ¶73.) Not only that, Quake's microfluidic device would use a lesser amount of reagents than Haff's capillary system. (*Id.*, ¶74.) And a POSA would have had a reason to conserve reagents to reduce costs and to minimize the amount of sample DNA needed, for example. (*Id.*) Thus, a POSA would have had a reason to modify Haff's method to use the microfluidic "droplet" system taught in Quake as opposed to the capillary "slug" system taught in Haff. (*Id.*, ¶¶73-74) And a POSA would have had a reasonable expectation of success in so doing because Quake teaches that his microfluidic device designs can be used to perform PCR. (*Id.*, ¶75.)

For example, Haff and Quake are both directed to performing enzymatic reactions, such as PCR, in small volumes of aqueous fluids. (GEN1021, 9:56-63 and Fig. 2; GEN1004, ¶¶[0015], [0080], [0113], [0290]; *see* GEN1005, 6:17-19, 24:12-13, 34:26-29, 82:23-83:4; GEN1002, ¶55.) Haff teaches performing PCR—an autocatalytic reaction—in a capillary thermal cycler by injecting into a main

channel via syringe alternating slugs of (1) an aqueous PCR reaction mixture comprised of, *inter alia*, target DNA—*i.e.*, a substrate molecule—along with primers, enzymes, and dNTPs—*i.e.*, reagents for conducting the autocatalytic reaction—and (2) an immiscible fluid, such as mineral oil. (GEN1021, 1:12-15, 1:21-27, 9:56-63, 10:20-35, Fig. 2; GEN1002, ¶¶56, 60-63.) Figure 2 from Haff, reproduced below, illustrates the design of Haff's system.



Haff discloses routing the main channel “in and out of hot and cold sources of the appropriate temperature,” which provides conditions suitable for the autocatalytic reaction to occur by reacting the target DNA with the primers, enzymes, and dNTPs once the reaction mixture enters the appropriate temperature zone—aiding in amplification of the target DNA. (GEN1021, 1:12-15, 9:55-10:6, 10:15-19; GEN1002, ¶64.) Haff discloses operating the injection syringes by hand, compressed gas, or a pump. (GEN1021, 10:25-28; GEN1002, ¶63.) However, Haff's slugs of PCR reaction mixture are not described as being surrounded by the

immiscible fluid. (GEN1002, ¶65.) Thus, a POSA would have been concerned that Haff's slugs may adhere to the channel walls and lose reagents due to diffusion of the reagents out of the slug. (*Id.*)

Quake teaches a microfluidic system for performing a reaction within an aqueous droplet. (GEN1004, Abstract, ¶¶[0015], [0018], [0080], [0106], [0314]-[0318]; *see* GEN1005, Abstract, 6:25-27, 7:20-8:5, 24:12-16, 32:14-16, 84:12-85:25; GEN1002, ¶57.) A POSA would have had a reason to practice Haff's PCR method in a microfluidic device, which is smaller than the capillary device in Haff, in order to reduce the amount of reactants needed. (GEN1033, 484:1; GEN1015, 271:1; GEN1002, ¶65.) Additionally, 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. (GEN1004, Abstract, ¶¶[0006], [0014], [0094]; *see* GEN1005, Abstract, 3:80-14, 6:3-5, 28:21-26; GEN1002, ¶¶66-67.) Quake teaches that his method overcomes such drawbacks by using microfluidic devices to create aqueous droplets that do not adhere to the channel wall and limit the diffusion of reagents. (GEN1004, ¶¶[0012]-[0015], [0290]; *see* GEN1005, 5:12-7:10, 82:23-83:4; GEN1002, ¶66.)

As such, a POSA would have had a reason to modify Haff's method of amplifying a target DNA sequence by performing PCR in slugs of aqueous fluid to use Quake's method of performing PCR in microfluidic droplets that contain a

single biological molecule. (GEN1002, ¶73.) This is because 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.*)

Quake's droplets meet the definition of the plugs of the '193 patent discussed in § V, above. (*Id.*, ¶68.) For instance, Quake discloses controlling the force and direction of the fluids flowing in the inlet and main channels, such that droplets of aqueous fluid are sheared off into the flow of the oil in the main channel at the junction of the inlet channel and the main channel. (GEN1004, ¶¶[0015], [0125], [0290], [0287], Fig. 16; *see* GEN1005, 6:17-19, 7:7-10; 38:16-19, 82:2-3, Fig. 16; GEN1002, ¶68.) And according to Quake, when using the microchannels taught in Quake, the droplets formed will "conform to the size and shape of the channels, while maintaining their respective volumes." (GEN1004, ¶[0092]; *see* GEN1005, 28:4-6; GEN1002, ¶68.) Further, Quake discloses that the sheared off droplets of aqueous fluid are encapsulated, *i.e.*, substantially surrounded, by the oil in the main channel, such that the oil would form a thin film between the aqueous droplet and the microfluidic channel wall. (GEN1004, ¶[0100], GEN1005, 30:2-3; GEN1002, ¶¶68-69.) This is because Quake's droplets "conform to the size and shape of the channels." (GEN1004, ¶[0092]; *see* GEN1005, 28:4-6; GEN1002, ¶¶68-69.)

Thus, a POSA would have recognized that Quake's droplets are the same as

the '193 patent's plugs. (*See* § V, above; GEN1002, ¶¶68-69.) So, a POSA, having a reason to modify Haff's "slug" method to instead use the "droplets" taught in Quake, would have arrived at the claimed method of performing an autocatalytic reaction, such as PCR, in "plugs" of aqueous fluid. (GEN1002, ¶¶73-75.)

In addition, Quake discloses that the aqueous fluid sample concentration can be optimized to obtain plugs that "contain no more than a single molecule ... with only a small statistical chance that a droplet will contain two or more molecules...." (GEN1004, ¶[0120]; *see* GEN1005, 37:12-19; GEN1002, ¶71.) And indeed, Quake teaches generating plugs containing a single biological molecule is an advantage of his method. (GEN1004, ¶[0015]; *see* GEN1005, 6:29-7:5; GEN1002, ¶66.) Additionally, Quake teaches that his method can be used to detect and analyze target polynucleotide sequences, and that his method can be adapted to perform PCR. (GEN1004, Abstract, ¶¶[0062], [0063], [0080]; *see* GEN1005, 17:19-18:21, 24:12-13; GEN1002, ¶72.) As such, a POSA, having a reason to modify Haff's capillary method of performing PCR to use the microfluidic method taught in Quake, would have arrived at the method recited in claim 1. (GEN1002, ¶¶73-74.)

Moreover, a POSA would have had a reasonable expectation of successfully doing so because it would have required no more than routine skill and knowledge in the art 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. (*Id.*, ¶75.) This is because Quake teaches how to obtain aqueous plugs that contain a single substrate molecule, and microfluidic device designs capable of so doing. (GEN1004, ¶¶[0015], [0084], [0100], [0120], [0125], [0020], [0290], [0292], Fig. 16; *see* GEN1005, 6:17-19, 7:7-10, 25:7-22, 30:2-3, 37:12-19, 38:16-19, 8:18-21, 82:27-83:1, 83:8-16, Fig. 16; GEN1002, ¶75.) And Quake teaches microfluidic device designs capable of sheering the aqueous fluid into oil encapsulated plugs, such that the plugs are separated from the channel wall by a thin layer of oil—resulting in a lack of adherence of the plug to the channel wall. (*See, e.g.*, GEN1004, ¶¶[0084], [0094], [0292], Fig. 16; GEN1005, 25:7-22, 35:28-3, 83:8-16, Fig. 16; GEN1002, ¶75.) Based on these detailed teachings in Quake, a POSA would have reasonably expected to successfully modify Haff’s method of alternatively injecting aqueous fluid containing substrate molecules and reagents and then oil to use Quake’s method of flowing an aqueous fluid containing a reagent in to a flowing stream of oil. (GEN1002, ¶75.)

Claim 2 depends from claim 1 and recites that “the at least one substrate molecule is a single biological molecule.” (GEN1001, 78:30-31.) **Claim 3** depends from claim 2 and recites that “the at least one substrate molecule is DNA and the

autocatalytic reaction is a polymerase-chain reaction.” (*Id.*, 78:32-34.)

Haff discloses performing PCR, an autocatalytic reaction that involves the amplification of DNA, *i.e.*, a substrate molecule that is a biological molecule. (GEN1021, 1:12-37, 9:55-10:56; GEN1002, ¶79.) And as discussed above, Quake discloses obtaining plugs that “contain no more than a single molecule ... with only a small statistical chance that a droplet will contain two or more molecules....” (GEN1004, ¶[0120]; *see* GEN1005, 37:12-19; GEN1002, ¶82.) Moreover, Quake teaches generating plugs containing a single biological molecule is an advantage of his method. (GEN1004, ¶[0015]; *see* GEN1005, 6:29-7:5; GEN1002, ¶82.) So, in addition to the reasons outlined above for claim 1, a POSA would have had a reason to arrive at the method of claims 2 and 3 in view of Haff and Quake, because they both teach performing PCR—an autocatalytic reaction that uses biological molecules—in their systems. (GEN1021, 9:56-10:56; GEN1004, ¶[0080]; *see* GEN1005, 24:12-13; GEN1002, ¶83.)

Moreover, a POSA would have done so with a reasonable expectation of success, given that Haff teaches performing PCR and Quake teaches that his method can be used to generate plugs containing a single biological molecule. (GEN1021, 9:56-10:56; GEN1004, ¶[0120]; *see* GEN1005, 6:29-7:5; GEN1002, ¶84.) Further, Quakes teaches that his method can be used to detect and analyze target polynucleotide sequences, and be adapted to perform PCR. (GEN1004,

Abstract, ¶¶[0062], [0063], [0080]; *see* GEN1005, 17:19-18:21, 24:12-13; GEN1002, ¶84.)

Claim 4 depends from claim 1 and recites that the “the step of providing conditions includes heating.” (GEN1001, 78:35-36.) Haff discloses a microfluidic device and method for performing PCR. (GEN1021, 9:61-10:6; GEN1002, ¶88.) In Haff’s device, the microfluidic channel passes through hot and cold zones to denature and subsequently amplify the target DNA. (GEN1021, 1:61-64, 9:61-10:6, 10:15-19, 10:48-51, Fig. 2; GEN1002, ¶88.) So, in addition to the reasons outlined above for claim 1, a POSA would have had a reason to provide heat when performing PCR, as recited in claim 4, and would have done so with a reasonable expectation of success. (GEN1002, ¶89.)

Claim 5 requires that the method of claim 1 further comprises “the step of providing a detector to detect, analyze, characterize, or monitor one or more properties of the autocatalytic reaction during and/or after it has occurred.” (GEN1001, 78:37-40.)

Haff discloses providing a detector to monitor the growth of the PCR product while performing a PCR reaction. (GEN1021, 8:18-27, 25:34-44, 26:1-6, 26:23-26; GEN1002, ¶93.) For instance, Haff discloses providing a fluorescence detector to monitor TaqMan based PCR assays, which utilize fluorescently labeled polynucleotides to detect the relative quantity of a target DNA sequence in a PCR

reaction mixture. (GEN1021, 8:25-27, 26:1-16; GEN1002, ¶93.) Furthermore, Haff discloses that the detector can be adapted to function on various microfluidic devices. (GEN1021, 26:23-26; GEN1002, ¶93.) And a POSA would have been readily able to adapt a detector. (GEN1002, ¶95.) Likewise, Quake discloses providing a detector that can detect a signal produced by the interaction of biological materials within Quake's plugs as they pass through a detection region. (GEN1004, ¶¶[0016], [0018]; *see* GEN1005, 7:11-14, 8:3-5; GEN1002, ¶94.) So, in addition to the reasons outlined above for claim 1, a POSA would have had a reason to arrive at the method of claim 3, and would have done so with a reasonable expectation of success. (GEN1002, ¶95.)

Claim 7 depends from claim 1 and requires that the carrier fluid comprises a surfactant. (GEN1001, 78:42-43.) **Claim 8** depends from claim 7 and requires that the surfactant is a fluorinated surfactant. (*Id.*, 78:44-45.) Quake discloses that his carrier fluid "may contain additives, such as agents which reduce surface tensions (surfactants)," and that "[e]xemplary surfactants include ... fluorinated oils." (GEN1004, ¶¶[0094], [0096], [0117], [0118]; *see* GEN1005, 28:21-23, 35-28-36:1, 36:8-10; GEN1002, ¶98.) And Quake teaches the benefits of including surfactants in the carrier fluid, such as preventing cells, or other particles and molecules from adhering to the sides of the channel, and controlling or optimizing droplet size, flow and uniformity, for example. (GEN1004, ¶¶[0094] and [0117]; *see* GEN1005,

28:21-26, 35:28-36:1; GEN1002, ¶98.) Thus, a POSA reading Quake’s disclosure would have chosen a surfactant that is a fluorinated oil, *i.e.*, a fluorinated surfactant. (GEN1002, ¶98.) Quake also discloses including surfactants to reduce surface tensions and to prevent adherence of the plugs to the channel walls. (GEN1004, ¶¶[0094], [0096], [0117]; *see* GEN1005, 35:28-36:1; GEN1002, ¶99.) So, in addition to the reasons outlined above for claim 1, a POSA would have had a reasonable expectation of success in adding a surfactant, including a fluorinated oil surfactant, to the carrier fluid, because Quake teaches such a method. (GEN1002, ¶99.)

Patent Owner may argue that claims 7 and 8 are distinguishable from Quake by repeating in this proceeding an argument it made during the prosecution of related U.S. Patent No. 8,889,083. There, the Examiner rejected a claim requiring that the aqueous plug be “substantially surrounded” by carrier fluid comprising a fluorinated oil. (GEN1036, p. 1064.) The Examiner reasoned that Quake met this limitation by disclosing that the plugs are surrounded by channel walls that are coated with fluorinated oil. (*Id.*) In response, Patent Owner amended the term “substantially surrounded” to instead read “substantially encased,” and argued: “As the Examiner concedes, the fluorinated oil in Quake is *only on the wall of the channel.*” (*Id.*, p.1064 (emphasis added).)

But this argument mischaracterizes Quake by ignoring his disclosure that the carrier fluid, which is preferably an oil, “may contain *additives, such as agents which reduce surface tensions (surfactants)*. Exemplary surfactants include ... fluorinated oils.” (GEN1004, ¶[0117] (emphasis added); *see* GEN1005, 35:28-29; GEN1002, ¶100.) Therefore, Quake does not limit the presence of surfactants to only as a coating on the channel wall. (GEN1002, ¶100.) Rather, Quake discloses that the surfactant can also be present in the carrier fluid. (GEN1004, ¶[0117]; *see* GEN1005, 35:28-29; GEN1002, ¶100.) And nevertheless, Quake’s plugs—like those of the ’193 patent—would be separated from the channel wall by a thin film of surfactant-containing carrier fluid that also coats the channel walls (*see* § V, above). (GEN1002, ¶100.) Thus, any similar argument from Patent Owner during this proceeding would likewise be improper and should be ignored.

Claim 9 depends from claim 1 and recites that “the at least one plug is a merged plug.” (GEN1001, 78:46-47.) As discussed above in § V, a POSA would understand that a merged plug can be formed by varying the relative velocity of the different plugs relative to each other and by varying the location of plug-fluid inlet ports. (GEN1002, ¶44.)

Quake discloses his droplets “can be ... combined with other droplets (e.g. to react droplet contents).” (GEN1004, ¶[0012], [0059]; *see* GEN1005, 5:21-22, 16:4-7; GEN1002, ¶104.) Quake further discloses that

the device may comprise *a first inlet region* in communication with the main channel *at a first droplet extrusion region*, and *a second inlet region* in communication with the main channel *at a second droplet extrusion region*. A fluid containing a first biological material may pass through the first inlet region so that *droplets of the fluid containing the first biological material are sheared into the main channel*. A fluid containing a second biological material may pass through the second inlet region so that *droplets of the fluid containing the second biological material are sheared into the main channel*. In various aspects, *the droplets of the first material may mix or combine with the droplets of the second biological material*, and the first and second biological materials may interact with each other upon mixing. (GEN1004, ¶[0018] (emphasis added); see GEN1005, 7:22-8:1 (emphasis added); GEN1002, ¶104.) And Quake discloses that “[t]he introduction of droplets through the different extrusion regions may be controlled, e.g., so that the droplets combine.” (GEN1004, ¶[0119]; see GEN1005, 37:3-5; GEN1002, ¶104.) Further, Quake provides an exemplary method of controlling the introduction of droplets, so that they combine:

In the preferred embodiment illustrated in FIG. 22, ... droplets containing the enzyme are first sheared off into the main channel 2201 at the first droplet extrusion region 2204. These droplets then [sic] move downstream, with the oil stream in the main channel, and pass through the second droplet extrusion region 2205. Droplet[s] containing the substrate are also sheared off into the main channel, at the second droplet extrusion region. By timing release of these

droplets to occur as a droplet of enzyme passes through the second droplet extrusion region, the two droplets are combined and the enzyme is able to react with the substrate.

(GEN1004, ¶[0316] and Fig. 22; *see* GEN1005, 84:28-85:10; GEN1002, ¶104.)

Therefore, Quake discloses the formation of merged plugs because Quake discloses (1) controlling the introduction of droplets by varying the relative velocity of the different plugs relative to each other, *e.g.* by timing the release of each droplet and (2) varying the location of plug-fluid inlet ports. (*See, e.g.*, GEN1004, ¶¶[0119], [0316] and Fig. 22; GEN1005, 37:3-5, 84:28-85:10; GEN1002, ¶105.)

A POSA reading Haff in view of Quake would have had a reason to merge plugs. (GEN1002, ¶106.) This is because Quake teaches forming a first droplet containing an enzyme and a second droplet containing a substrate for the enzyme. (GEN1004, ¶¶[0018], [0316] and Fig. 22; *see* GEN1005, 7:22-8:1 84:28-85:10; GEN1002, ¶106.) And combining the droplets would allow the enzyme to react with the substrate. (GEN1004, ¶[0018]; *see* GEN1005, 7:22-8:11 GEN1002, ¶106.) Further, a POSA would have understood that initially keeping an enzyme separated from its substrate would have allowed one to control, for instance, the timing of the reaction. (GEN1002, ¶106.)

Moreover, a POSA would have had a reasonable expectation of success doing so because Quake teaches methods for keeping an enzyme and its substrate

separated by generating two different plugs—one containing an enzyme and another containing its substrate. (GEN1004, ¶¶[0018], [0119], [0316]; *see* GEN1005, 7:22-8:1, 36:29-37:3, 84:28-85:10; GEN1002, ¶106.) And Quake teaches initiating the reaction by merging the plug containing the enzyme with a plug containing its substrate. (GEN1004, ¶[0316]; *see* GEN1005, 84:28-85:10; GEN1002, ¶106.) So, in addition to the reasons outlined above for claim 1, a POSA would have had a reason to arrive at the method of claim 9, and would have done so with a reasonable expectation of success. (GEN1002, ¶106.)

Claim 11 depends from claim 1 and recites that “the at least one plug is substantially spherical in shape.” (GEN1001, 78:51-52.) As discussed in § V, a POSA would understand that a spherical plug is formed in a round channel that expands downstream of the droplet extrusion region. (GEN1002, ¶¶46-47, 110.)

Quake discloses that his devices can “generate *round*, monodisperse droplets,” and that “[d]roplet dimensions and flow characteristics can be influenced as desired, in part by changing the channel dimensions, e.g. the channel width.” (GEN1004, ¶¶[0092], [0093], Fig. 17A; *see* GEN1005, 28:19-20, Fig. 17A; GEN1002, ¶111.) In addition, Quake discloses using round channels provides an advantage of facilitating an orderly flow of droplets in the channels. (GEN1004, ¶[0091]; *see* GEN1005, 27:22-27; GEN1002, ¶111.) Quake further teaches tapering the width of the main channel at the droplet extrusion region and then

expanding it downstream of the droplet extrusion region. (GEN1004, ¶¶[0292], [0315], Figs. 16B and 22; *see* GEN1005, 83:13-16, 84:16-24, Figs. 16B and 18; GEN1002, ¶111.)

A POSA reading Haff in view of Quake would have had a reason to use a round channel. (GEN1002, ¶112.) This is because Quake teaches round channels are advantageous because they facilitate an orderly flow of droplets in the channels. (GEN1004, ¶[0091]; *see* GEN1005, 27:22-27; GEN1002, ¶112.) Moreover, Quake discloses that his method forms round droplets by changing the channel width. (GEN1004, ¶¶[0092], [0093]; *see* GEN1005, 28:19-20; GEN1002, ¶112.) Thus, a POSA would have understood from Quake’s teachings that Haff’s device modified in view of Quake—comprising a round main channel that is expanded downstream from the droplet extrusion region—would produce a plug that is substantially spherical in shape. (GEN1004, ¶¶[0091], [0292], [0315], Figs. 16B and 22; *see* GEN1005, 27:22-27, 83:13-16, 84:16-24, Figs. 16B and 18; GEN1002, ¶112.) This is because a POSA would understand that a plug substantially spherical in shape encompasses Quake’s disclosed “round” plugs, which are plugs present in a round expanded channel. (*See* § V, above; GEN1002, ¶112.) So, in addition to the reasons outlined above for claim 1, a POSA would have had a reason to arrive at the method of claim 11, and would have done so with a reasonable expectation of success. (GEN1002, ¶112.)

B. Ground 2: Claim 6 would have been obvious over Haff in view of Quake, and further in view of Ramsey

As supported by the declaration of Dr. Huck, claim 6 would have been obvious over Haff (GEN1021) in view of Quake (GEN1004), and further in view of U.S. Patent No. 6,524,456 (“Ramsey”) (GEN1006). (GEN1002, ¶¶113-124.) Ramsey was filed by another on September 29, 1999 and issued on February 25, 2003. Thus, Ramsey qualifies as prior art under 35 U.S.C. § 102(e) to the ’193 patent claims as of its September 29, 1999 filing date.

Claim 6 depends from claim 1 and requires that “the oil [recited in claim 1] is fluorinated oil.” (GEN1001, 78:58.) Ramsey, like Haff and Quake, is directed to performing enzymatic reactions in small volumes of aqueous fluids. (GEN1002, ¶114.) Quake discloses that suitable immiscible carrier fluids include hydrocarbons “such as decane (e.g., tetradecane or hexadecane) or another oil (for example, mineral oil).” (GEN1004, ¶¶[0015], [0096]; *see* GEN1005, 6:21-23; GEN1002, ¶119.) Quake also discloses using fluorinated oils as surfactants in the carrier fluid. (GEN1004, ¶[0117]; *see* GEN1005, 35:28-36:1; GEN1002, ¶119.)

Ramsey teaches injecting minute volumes of a reaction fluid comprising a biological molecule into a microchannel to perform enzymatic reactions. (GEN1006, 3:62-65, 8:45-9:19; GEN1002, ¶120.) Ramsey discloses separating the minute volumes of reaction fluid using a segmenting fluid that “is preferably a liquid that is immiscible in ... the reaction fluid[.]” (GEN1006, 3:63-67, 6:36-50;

GEN1002, ¶120.) Based on the description in Ramsey, a POSA would have considered Ramsey's segmenting fluid to serve the same purpose as the carrier fluid recited in the '193 patent claims. (GEN1002, ¶120.) And Ramsey teaches that "the segmenting fluid should be biocompatible with [the] biological reagents that are used" in the reaction fluid. (GEN1006, 6:36-50; GEN1002, ¶120.) In that regard, Ramsey discloses that "[p]erfluorocarbons [are] suitable because they are widely used where biocompatibility is required." (GEN1006, 6:36-50; GEN1002, ¶120.) Perfluorocarbons are fluorinated forms of hydrocarbons in which all the hydrogen-carbon bonds have been replaced by fluorine-carbon bonds. (GEN1002, ¶120.)

A POSA would have had a reason to modify Haff, in view of Quake and Ramsey, to use Ramsey's perfluorocarbons—*i.e.*, fluorinated oils—as an immiscible carrier fluid when performing enzymatic reactions, such as PCR. (GEN1002, ¶121.) This is because, as Ramsey states, using perfluorocarbons when biocompatibility is required was already well-known in the art by May 2002. (GEN1006, 6:36-50; GEN1002, ¶121.) Moreover, Ramsey explicitly teaches using perfluorocarbons as a carrier fluid because perfluorocarbons are biocompatible with the biological reagents used for performing the enzymatic reactions taught in Haff and Quake. (GEN1006, 6:36-50; GEN1002, ¶121.)

Further, a POSA would have had a reasonable expectation of successfully

doing so because it would have required no more than routine skill and knowledge in the art to adapt Haff's PCR device, as modified by Quake in view of Ramsey, to use Ramsey's method of using perfluorocarbons as the carrier fluid. (GEN1002, ¶122.) This is because both Quake's and Ramsey's methods disclose using carrier fluids to transport small volumes of aqueous fluids, wherein enzymatic reactions occur, in a microfluidic device. (GEN1004, ¶¶[0015], [0096]; *see* GEN1005, 6:21-23; GEN1006, 3:63-67, 6:36-50; GEN1002, ¶122.) Quake also discloses that hydrocarbons are suitable carrier fluids. (GEN1004, ¶[0096]; *see* GEN1005, 6:21-23; GEN1002, ¶122.) And Ramsey teaches that perfluorocarbons—which are fluorinated forms of hydrocarbons—are suitable carrier fluids because they are biocompatible with the biological reagents used in enzymatic reactions, such as PCR. (GEN1006, 6:36-50; GEN1002, ¶122.) Further, both Quake and Ramsey disclose using fluorinated oils in their methods. (GEN1004, ¶[0117]; *see* GEN1005, 35:38-36:1; GEN1006, 6:36-50; GEN1002, ¶122.)

C. Objective indicia do not support patentability

In addition to Petitioner's strong *prima facie* obviousness showing outlined above, objective indicia must be taken into account, although they do not necessarily control the obviousness conclusion. *See Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Objective evidence must be attributable to the claimed invention, and not attributable to what is unclaimed or

present in the prior art. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (finding that to be afforded substantial weight, objective indicia of nonobviousness must be tied to the novel elements of the claim at issue.) Even when there is substantial evidence of relevant objective indicia, such evidence may be inadequate to overcome a strong *prima facie* obviousness. *See, e.g., Leapfrog Enterprises Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Patent Owner raised no objective indicia of nonobviousness during prosecution of the '193 patent. (GEN1039.) To the extent Patent Owner may now argue that objective indicia exists based on acquiescence by licensing, commercial success, long-felt but unmet need, failure of others, industry praise, or unexpected superior results, any such arguments are unsupported by the available evidence and fail to weigh in favor of patentability in view of Petitioner's strong *prima facie* showing of obviousness. Also, Petitioner should be given an opportunity to rebut any objective indicia of nonobviousness that Patent Owner raises for the first time in this proceeding or in the parallel district court litigation.

1. No acquiescence by licensing

Licensing can evidence nonobviousness where (1) a nexus between the merits of the invention and the licenses exists and (2) proof exists that the license arose out of substantial industry recognition and acceptance of the patent's validity. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983)

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(“[Patent Owner] has shown neither a nexus between the merits of the invention and the licenses of record, nor that those licenses arose out of recognition and acceptance of the patent”); *see also Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 459 (D. Del. 2012), *aff’d in relevant part* 694 F.3d 1344, 1357 (Fed. Cir. 2012). And when licensing a patent is in the economic interest of the licensee, regardless of the validity of the patent, then the license does not suggest nonobviousness. *See EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907-08 (Fed. Cir. 1985) (“[Licensing] programs are not infallible guides to patentability. They sometimes succeed because they are mutually beneficial to the licensed group ... or for other reasons unrelated to the unobviousness of the licensed subject matter.”).

Patent Owner has exclusively licensed the ’193 patent to RainDance Technologies, Inc. (“RainDance”) (GEN1019, ¶¶3-4, 28.) However, there is no available evidence to suggest that RainDance entered the licensing agreement, not merely for RainDance’s economic interests, but instead in acquiescence to the merits of the alleged invention. Moreover, as RainDance is the only purported licensee of the ’193 patent, there is no evidence to suggest widespread industry recognition and acceptance of the ’193 patent through licensing by parties other than RainDance. Therefore, the available evidence does not show that acquiescence by licensing supports the patentability of the ’193 patent claims.

2. No commercial success

Patent Owner may assert that RainDance's RainDrop[®] system is a commercial embodiment of the '193 patent. As an initial matter, no available evidence demonstrates that the RainDrop[®] system either (i) practices the features claimed in the '193 patent or (ii) has substantially increased in market share, for example, by substantially expanding the market or by substantially displacing competing products in the market. But even if the RainDrop[®] system practices the features claimed in the '193 patent, any alleged commercial success of the system would be attributable to features that were present in the prior art. (GEN1002, ¶127.) For example, Quake discloses isolating single substrate molecules in an aqueous droplet in a microfluidic system. (*See, e.g.*, GEN1004, ¶[0015], [0020], [0120]; GEN1005, 6:29-7:1; GEN1002, ¶127.) And a POSA would have understood that conducting reactions, such as PCR, in microfluidic systems using small volumes of aqueous fluid surrounded by a carrier fluid was well-known in the art before May 2002. (*See, e.g.*, GEN1004, ¶¶[0018], [0080], [0317], [0318]; GEN1005, 8:14-9:2, 24:12-13, 85:12-25; GEN1006, 8:45-9:63; GEN1011, pp. 2-8; GEN1002, ¶127) Therefore, the available evidence does not show that any alleged commercial success of the RainDrop[®] system—or any other product—supports the patentability of the '193 patent claims. *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1345 (Fed. Cir. 2007) (where a product's commercial success can be attributed to

characteristics of the invention that were already in the prior art, nonobviousness is not shown.)

3. No long-felt but unmet need or failure of others

A showing of a long-felt and unmet need requires that the need must have been a persistent one that was recognized by those of ordinary skill in the art. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). Also, the long-felt need must not have been satisfied by another before the invention. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc.*, 976 F.2d 1559, 1574-75 (Fed. Cir. 1992). And the invention must in fact satisfy the long-felt need. *Id.* at 1575. Failure of others to find a solution to the problem which the patent purports to solve is also relevant in determining nonobviousness. *Id.*

There was no long-felt but unmet need or failure of others to make a microfluidic reaction device by May 2002. As discussed in § IV.A.2. above, several microfluidic reaction devices existed before May 2002. (GEN1002, ¶129.) And devices for forming stable, aqueous plugs in carrier fluids were also known at that time. (GEN1004; GEN1005; GEN1010; GEN1018; GEN1011; GEN1002, ¶129.) There is no available evidence that these prior art devices failed to satisfy a need or solve a problem that was allegedly met or solved by the features claimed in the '193 patent. (GEN1002, ¶129.) Therefore, the available evidence does not show that a long-felt but unmet need or a failure of others supports the

patentability of the '193 patent claims.

4. No industry praise

Praise for an invention by peers in the industry may support nonobviousness, but only if such praise is directed to claimed features of the invention and not to elements found in the prior art. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1365-66 (Fed. Cir. 2007).

Although the RainDrop[®] system was named among the “Top Ten Innovations of 2014” by the magazine *The Scientist*, there is no evidence that the award is attributable to the methods recited in the '193 patent claims. (GEN1020.) And to the extent that Patent Owner contends that this recognition is attributable to features claimed in the '193 patent, these features were taught in the prior art. (*See, e.g.*, GEN1004, ¶[0013]; GEN1005, 5:19-23; GEN1011, pp. 2-8; GEN1002, ¶131) As such, this recognition by *The Scientist* should be given no weight in a nonobviousness analysis. *In re Kao*, 639 F.3d at 1068. And Petitioner is not aware of any other evidence of praise in the industry that weighs in favor of patentability. (GEN1002, ¶132.) Therefore, the available evidence does not show that industry praise supports the patentability of the '193 patent claims.

5. No unexpectedly superior results

Nonobviousness of an invention can be demonstrated by showing that the claimed invention exhibits a superior property or advantage, *i.e.*, unexpectedly

superior results, over the closest prior art. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) Unexpectedly superior results must be commensurate in scope with the claims. *In re Boesch*, 617 F. 2d 272, 277 (C.C.P.A. 1980); *In re Peterson*, 315 F.3d 1325, 1329-31 (Fed. Cir. 2003).

Patent Owner may allege that the RainDrop[®] system's performance is unexpectedly superior compared to that of prior art microfluidic systems, and that such unexpectedly superior performance is attributable to alleged inventions claimed in the '193 patent. But as discussed above, the prior art disclosed isolating single substrate molecules in an aqueous plug and conducting reactions, such as PCR, in microfluidic systems using small volumes of aqueous fluid surrounded by a carrier fluid. (*See, e.g.*, GEN1004, ¶¶[0018], [0015], [0317], [0318]; GEN1006, 8:45-9:63; GEN1011, pp. 2-4; GEN1002, ¶134.) As such, no available evidence demonstrates that the RainDrop[®] system uses features claimed in the '193 patent to perform these same steps with unexpectedly superior results compared to those obtained using the devices and methods disclosed in the prior art. (GEN1002, ¶134.) Therefore, the available evidence does not show that unexpected superior results support the patentability of the '193 patent claims.

VII. Conclusion

Each of claims 1-9 and 11 would have been obvious over the art discussed above. Each of Ground 1 and Ground 2 amply demonstrates that a POSA would

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have arrived at claims 1-9 and 11 with a reasonable expectation of success. Indeed, claims 1-9 and 11 are no more than a combination of well-known prior art elements that yields predictable results. And nothing in claims 1-9 and 11 would have required an advancement over known methods. Moreover, no objective indicia of nonobviousness weigh in favor of patentability. Thus, Petitioner is reasonably likely to prevail on the Grounds discussed herein. As such, the Board should institute IPR for each challenged claim.

VIII. Mandatory notices (37 C.F.R. § 42.8(a)(1))

Real Party-In-Interest (37 C.F.R. § 42.8(b)(1)): 10X Genomics, Inc.

Related Matters (37 C.F.R. § 42.8(b)(2)): **Judicial:** *RainDance Techs., Inc., et al. v. 10X Genomics, Inc.*, 1:15-cv-00152-RGA (D. Del. Feb. 2, 2015).

Administrative: Petitioner is concurrently filing petitions for IPR of U.S. Patent Nos. 8,273,573; 8,822,148; 8,329,407, and 8,889,083.

Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead Counsel	Back-Up Counsel
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Notice of Service Information (§ 42.8(b)(4)): Please direct all

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correspondence to lead and back-up counsel at the above address. Petitioner consents to email service at: eellison-PTAB@skgf.com and dsterlin-PTAB@skgf.com.

Procedural Statements: This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed are a Power of Attorney and Exhibit List under 37 C.F.R. § 42.10(b) and § 42.63(e), respectively. The required fee is paid through online credit card payment. The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

Respectfully submitted,
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Petition for Inter Partes Review of U.S. Patent No. 8,304,193

CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned “Petition for *Inter Partes* Review of U.S. Patent No. 8,304,193 under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123,” including its supporting evidence (Exhibits 1001-1042), was served in its entirety on May 6, 2015, upon the following parties via FedEx:

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