

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 B2

Before DONNA M. PRAISS, CHRISTOPHER L. CRUMBLEY, and
TINA E. HULSE, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

10X Genomics, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–9 and 11 of U.S. Patent No. 8,304,193 B2 (Ex. 1001, “the ’193 patent”). Paper 2 (“Pet.”). The University of Chicago (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 9 (“Prelim. Resp.”).

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon considering the Petition and Preliminary Response, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–9 and 11. Accordingly, we decline to institute an *inter partes* review of those claims.

A. *Related Proceedings*

Petitioner identifies as a related matter *RainDance Techs., Inc. v. 10X Genomics, Inc.*, No. 1:15-cv-00152-RGA (D. Del.). Pet. 55.

Petitioner has also concurrently filed petitions for *inter partes* review of related patents in IPR2015-01162 (US 8,273,573), IPR2015-01158 (US 8,329,407), IPR2015-01157 (US 8,889,083), and IPR2015-01156 (US 8,822,148).

B. *The ’193 Patent (Ex. 1001)*

The ’193 patent relates to a method for conducting an autocatalytic reaction in plugs in a microfluidic system. Ex. 1001, Title. Microfluidic systems transport fluids through networks of

channels, typically having micrometer dimensions. *Id.* at 1:20–22. According to the Specification, the main advantages of microfluidic systems are high speed and low consumption of reagents. *Id.* at 1:25–26. The microfluidic systems may be used for various chemical and biochemical processes, including autocatalytic reactions, such as the polymerase chain reaction. *Id.* at 44:38–61.

Rather than rely on laminar flow of liquids through microfluidic channels, the '193 patent Specification describes using microfluidic droplets, or “plugs” in the system. Figure 2A-2, an embodiment of the system, is annotated and is reproduced below:

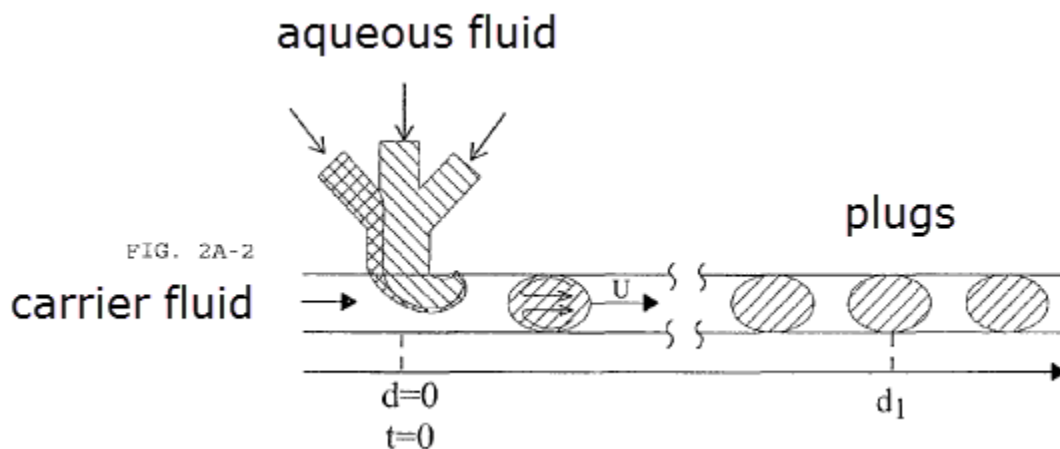


Figure 2A-2 depicts the formation of plugs, where the aqueous fluid containing a substrate and reagents enters a channel with an immiscible carrier fluid, such as an oil, to form a series of plugs. *Id.* at 17:38–43. The plug volumes, which are dependent on channel size, can range from about 1 femtoliter to about 250 nanoliters. *Id.* at 19:45–54.

C. Illustrative Claim

Petitioner challenges claims 1–9 and 11 of the '193 patent. Claim 1, the only independent claim, is illustrative and is reproduced below:

1. A method for conducting an autocatalytic reaction in plugs in a microfluidic system, comprising the steps of:

providing the microfluidic system comprising at least two channels having at least one junction;

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;

flowing an oil through the second channel of the at least two channels;

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

providing conditions suitable for the autocatalytic reaction in the at least one plug such that the at least one substrate molecule is amplified.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–9 and 11 of the '193 patent on the following grounds:

References	Basis	Claims challenged
Haff ¹ and Quake ²	§ 102	1–5, 7–9, and 11
Haff, Quake, and Ramsey ³	§ 103	6

II. ANALYSIS

A. Person of Ordinary Skill in the Art

The parties dispute the proper definition of a person of ordinary skill in the art. Petitioner contends that a person of ordinary skill in the art 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.

Pet. 3. Alternatively, Petitioner asserts that a skilled artisan would have had an M.S. or bachelor's degree in one of those disciplines with four or five years of additional relevant experience, respectively. *Id.* Patent Owner disagrees with Petitioner's definition, arguing that Petitioner overstates the level of ordinary skill in the art in the 2002 time frame. According to Patent Owner, a person of ordinary skill in the art would have been a researcher interested in microfluidics with at least a bachelor's degree in a "hard science," such as chemistry,

¹ Haff et al., US 6,033,880, issued Mar. 7, 2000 (Ex. 1021).

² Quake et al., US 2002/0058332 A1, published May 16, 2002 (Ex. 1004).

³ Ramsey et al., US 6,524,456 B1, issued Feb. 25, 2003 (Ex. 1006).

physics, chemical engineering, bioengineering, or mechanical engineering. Prelim. Resp. 34–35.

For purposes of this Decision, we do not discern an appreciable difference between Petitioner and Patent Owner’s proposed levels of ordinary skill in the art that would impact our ultimate conclusions. Patent Owner does not indicate how many years of experience a “researcher interested in microfluidics” would have. Accordingly, we determine that a person of ordinary skill in the art would have at least a bachelor’s degree in chemistry, physics, chemical engineering, bioengineering, or mechanical engineering, or a related discipline, with at least four or five years of relevant experience. We also consider the cited prior art as representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (finding the absence of specific findings on “level of skill in the art does not give rise to reversible error ‘where the prior art itself reflects an appropriate level and a need for testimony is not shown’”) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1276–80 (Fed. Cir. 2015); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d

1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. “*plug of the aqueous fluid*”

Claim 1 requires forming at least one “plug of the aqueous fluid.” Petitioner asserts that the broadest reasonable interpretation of this term is “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 by a thin film of carrier fluid.” Pet. 13. Patent Owner disagrees, asserting that the term should be construed to mean “volumes of aqueous fluid formed when a stream of aqueous fluid is introduced into the flow of a substantially immiscible carrier-fluid.” Prelim. Resp. 19.

At this stage of the proceeding, we find Patent Owner’s proposed construction more persuasive because it is more consistent with the Specification’s definition of “plugs.” The Specification states: “‘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.” Ex. 1001, 9:27–30. To further limit the claim term, Petitioner relies on the Specification’s disclosure of other optional characteristics of a plug. For example, the Specification states that the plug’s “cross-section *should be* substantially similar to the cross-section of the channels in which they are formed.” *Id.* at 9:34–37 (emphasis added). The Specification also states that the carrier fluid “preferably” wets

the walls of the channels and, “[i]f this condition is satisfied, the plug . . . remains separated from the walls by a thin layer of the carrier-fluid.” *Id.* at 20:59–63 (emphasis added). Because neither of these disclosures expressly limits the “plugs” of the claimed invention, we decline to include these limitations from the Specification in the broadest reasonable interpretation of the claim term.

Accordingly, on the current record, we determine the broadest reasonable interpretation of the term “plugs of the aqueous fluid” to be “volumes of aqueous fluid formed when a stream of aqueous fluid is introduced into the flow of a substantially immiscible carrier-fluid.”

2. *“conditions suitable for the autocatalytic reaction in the at least one plug such that the at least one substrate molecule is amplified”*

Claim 1 recites “providing conditions suitable for the autocatalytic reaction in the at least one plug such that the at least one substrate molecule is amplified.” Petitioner asserts that this limitation “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.” Pet. 14. Patent Owner disagrees with Petitioner’s construction to the extent that it simply requires a single stimulus to induce an autocatalytic reaction (regardless of whether that stimulus is sufficient to induce the reaction). Prelim. Resp. 21. According to Patent Owner, a skilled artisan would understand that the term refers “to a global set of physical and chemical conditions that allows one to conduct an autocatalytic reaction (including PCR) in droplets.” *Id.*

At this stage of the proceeding, we determine that Patent Owner's interpretation is more consistent with the plain and ordinary meaning of the claim term, which requires more than a single stimulus to induce a reaction. We are persuaded by Patent Owner's argument that the Specification sets forth certain conditions that must be addressed when conducting PCR in a microfluidic droplet, including unwanted adsorption of proteins on the surface of the droplet. Prelim. Resp. 20 (citing Ex. 1001, 35:59–66). Accordingly, we construe the claim term as requiring conditions that allow the substrate molecule to be amplified in a microfluidic system.

3. *Remaining Claim Terms*

Petitioner proposes constructions for other claim terms of the '193 patent. Based on the current record, however, we determine that the remaining claim terms need not be construed explicitly for purposes of this Decision.

C. *Obviousness over Haff and Quake*

Petitioner asserts that claims 1–5, 7–9, and 11 are unpatentable as having been obvious over Haff and Quake. Pet. 20–45. Petitioner relies on the testimony of its declarant, Wilhelm T. S. Huck, Ph.D. (Ex. 1002). Patent Owner opposes Petitioner's assertion. Prelim. Resp. 26–46. Based on the current record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the claims are unpatentable as having been obvious over the cited references.

1. *Haff (Ex. 1021)*

Haff relates to automated machines for performing amplification reactions for nucleic acids, such as a polymerase chain

reaction (“PCR”). Ex. 1021, 1:12–15. Haff states that PCR has been performed in disposable reaction tubes such as small, plastic microcentrifuge tubes or test tubes that are placed in an instrument containing a thermally controlled heat exchanger. *Id.* at 1:50–53. Haff explains that rapid, small-scale PCR capillary tube instruments have appeared in which the reaction mixture is placed in capillary tubes. *Id.* at 2:7–12. The Specification describes various capillary tube PCR instruments that use different means to heat and cool the PCR reaction mixture and different tube and fluid-handling means to move the reaction mixture.

Figure 2 of Haff is one embodiment and is reproduced below:

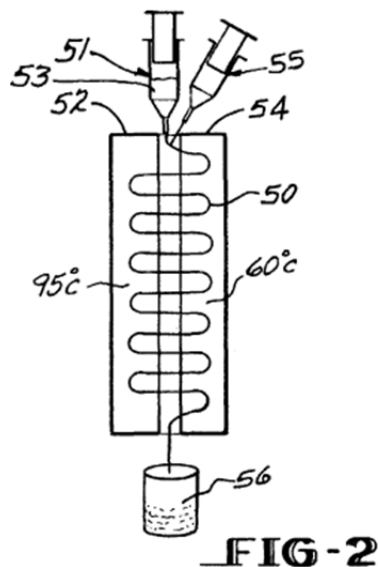


Figure 2 depicts a system that uses a length of capillary tubing 50 that is routed in and out of hot zone 52 and cool zone 54 a number of times. *Id.* at 9:58–65. Syringe 51, which contains PCR reaction mixture 53, and syringe 55, which contains air or an immiscible fluid, are connected in parallel with tubing 50. Ex. 1021, 10:20–32. Syringe 55 is operated intermittently to inject air bubbles or

immiscible fluid bubbles into the flow stream of reagent mixture 53 in tubing 50. *Id.* at 10:32–35. The use of bubbles between samples results in “slug” flow where sample “slugs” are passed through the capillary tubes. *Id.* at 9:50–52. According to Haff, “[th]e 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 the reaction mixture inside the tube are all factors in the control of the amplification.” *Id.* at 10:15–19.

2. *Quake (Ex. 1004)*

Quake relates to microfluidic devices and methods for analyzing and/or sorting biological materials. Ex. 1004, Abstract. Quake states that its device and methods “offer several advantages over traditional flow cytometry devices and methods.” *Id.* ¶ 14. Quake’s devices are designed to compartmentalize small droplets of aqueous solution within microfluidic channels filled with oil. *Id.* ¶ 3. The devices 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. *Id.* A junction joins the main channel with the sample inlet channel. *Id.* By adjusting the pressure of the oil and/or the aqueous solution, a pressure difference can be established such that the stream of aqueous solution is sheared off at a regular frequency as it enters the oil stream, thereby forming droplets. *Id.* Figure 16A of Quake is reproduced below:

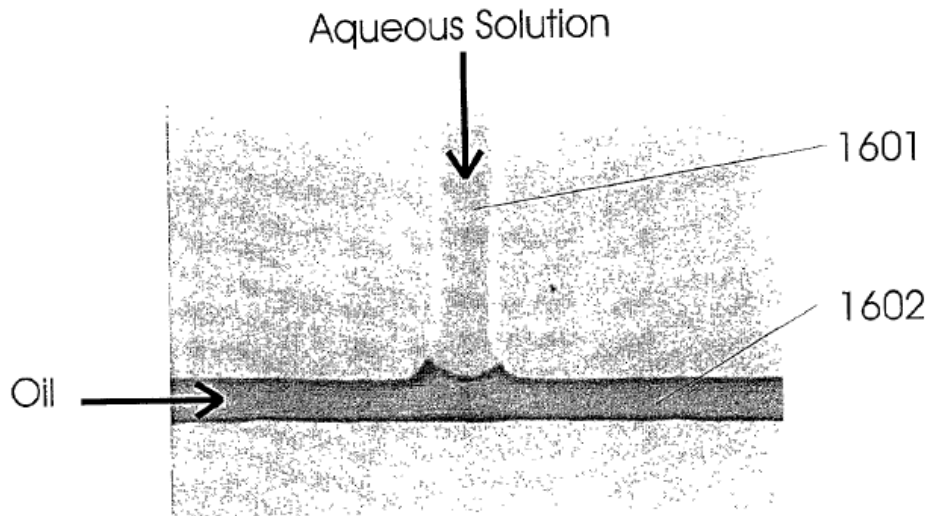


FIG. 16A

Figure 16A depicts the channel architecture for the droplet extrusion region. Channel 1601 containing an aqueous solution intersects with the main channel 1602 containing oil. Ex. 1004 ¶ 292.

In preferred embodiments, the droplets have a volume of approximately 0.1 to 100 picoliters. *Id.* According to Quake, microfabrication of the device “permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR.” *Id.* ¶ 80.

3. Analysis

Petitioner asserts that the combination of Haff and Quake teaches or suggests each limitation of claims 1–5, 7–9, and 11. Regarding claim 1, Petitioner provides a claim chart identifying the disclosures of Haff and Quake that purportedly teach or suggest each limitation.⁴ Pet. 21–30. For example, Petitioner asserts that Figure

⁴ We note that the claim chart identifies the last limitation of claim 1 as “providing conditions suitable for the reaction in the at least one plug involving the at least one biological molecule and the at least one

16A of Quake depicts a microfluidic system with two channels having one junction. Pet. 22–23 (citing Ex. 1004 ¶¶ 3, 292, Fig. 16A).

Petitioner also asserts that the combination of Haff’s PCR device and Quake’s microfluidics device suggests flowing the aqueous sample fluid and the oil through separate channels and forming a plug of aqueous sample fluid in the oil. Pet. 23–25 (citing Ex. 1021, 1:21–27, 10:20–35; Ex. 1004 ¶¶ 3, 14, 20, 120, 290, Fig. 16A). Quake teaches that the aqueous droplets are encapsulated, or substantially surrounded, by oil. Pet. 28 (citing Ex. 1004 ¶ 100). Finally, Petitioner asserts that the combination of Haff and Quake teach providing conditions suitable for the autocatalytic reaction in the plug such that at least one substrate molecule is amplified. Pet. 30 (citing Ex. 1021, 1:12–15, 9:55–10:2, 10:15–19; Ex. 1004 ¶ 80).

Petitioner then argues that a person of ordinary skill in the art would have had a reason to modify Haff’s method of PCR in capillary tube devices with the microfluidic device of Quake with a reasonable expectation of success. For example, Petitioner asserts that both references are directed to performing enzymatic reactions, such as PCR, in small volumes of aqueous fluids. *Id.* 31 (citing Ex. 1021, 9:56–63 and Fig. 2; Ex. 1004 ¶¶ 15, 80, 113, 290; Ex. 1002 ¶ 55). Petitioner also contends that a person of ordinary skill in the art would have had a reason to practice Haff’s PCR method in Quake’s

reagent to form a reaction product.” Pet. 30. The last limitation of claim 1, however, recites “providing conditions suitable for the *autocatalytic* reaction in the at least one plug *such that the at least one substrate molecule is amplified.*” Ex. 1001, claim 1 (emphasis added). Patent Owner did not object to the claim chart as incorrect. We, therefore, consider this to be a harmless typographical error.

microfluidic device to reduce the amount of reagents needed, which is beneficial when the availability of the reagents and substrate are limited. *Id.* at 33 (citing Ex. 1002 ¶ 65). According to Petitioner, the reason to combine Quake with a PCR method comes from Quake itself (*id.* at 35), which teaches that “[m]icrofabrication permits other technologies to be integrated or combined with flow cytometry on a single chip, such as PCR.” Ex. 1004 ¶ 80.

Petitioner argues that a person of ordinary skill in the art would have had a reasonable expectation of success in combining Haff and Quake. Pet. 35–36; Ex. 1002 ¶ 75. Dr. Huck explains that Quake teaches controlling the flow of oil and the flow of the aqueous sample fluid to generate an encapsulated stream of droplets. Ex. 1002 ¶ 75. Dr. Huck also states that Quake teaches adjusting the concentration of the biological molecule to ensure that the droplets contain no more than a single biological molecule and teaches that the device and method can be integrated with PCR. *Id.* Accordingly, Dr. Huck concludes:

[I]t would have required no more than routine skill and knowledge in the art for a [skilled artisan] to adapt Haff’s device to form a stream of PCR reaction mixture droplets encapsulated, *i.e.*, substantially surrounded by an oil, which droplets comprise a single substrate DNA molecule, and to conduct PCR amplification, an autocatalytic reaction, in the droplets to amplify the single substrate molecule.
Id.

In response, Patent Owner first argues that Haff is not analogous art because the field of the ’193 patent is microfluidic devices, and Haff involves larger volumes of fluids. Prelim. Resp. 26–28. Patent Owner also argues that Haff is not reasonably pertinent

to the problems being addressed in the '193 patent. *Id.* at 28–30. We are not persuaded. Although Haff does not disclose the use of PCR in microfluidic devices, we do not believe such disclosure is necessary to consider Haff to be analogous art. “A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor’s endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor’s attention in considering his problem.” *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1380–81 (Fed. Cir. 2007). On the current record, we find that Haff’s disclosure of PCR in larger-volume capillary tube devices logically would have commended itself to the inventors’ attention when considering methods of conducting PCR in smaller microfluidic devices. In other words, we find that the inventors logically would have considered how PCR is conducted in capillary tube devices to figure out how to scale down the reaction for microfluidic devices.

Patent Owner also argues that the Petitioner does not establish that one of ordinary skill in the art would have had a reasonable expectation of success combining Haff and Quake. Prelim. Resp. 37–46. In particular, Patent Owner challenges Petitioner’s assertion that the combination of Quake and Haff would have been “routine.” Patent Owner states that Petitioner’s assertion “is undermined by the lack of any reasoned explanation in the Petition for why this combination would have been successful.” *Id.* at 44–45.

We have considered Petitioner’s arguments and evidence together with the Preliminary Response, and, on this record, we agree with Patent Owner that Petitioner has not met the threshold for

instituting an *inter partes* review of the '193 patent. Petitioner and its declarant state that 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 . . . to perform PCR in a microfluidic device.” Pet. 35–36. But Petitioner cites insufficient evidence to support this statement. For example, Petitioner and its declarant assert that a skilled artisan would have had a reasonable expectation of success in doing so because “Quake teaches that his microfluidic device designs can be used to perform PCR.” *Id.* at 31 (citing Ex. 1002 ¶ 75); *see also id.* at 30 (citing Ex. 1004 ¶ 80 in claim chart). We are not persuaded, however, that such a conclusory statement by itself would have given a person of ordinary skill in the art a reasonable expectation of success in combining Haff and Quake.

We acknowledge that the Petition and Dr. Huck provide an overview of the state of the art as of May 2002. Pet. 4–10; Ex. 1002 ¶¶ 16–26. For example, the Petition describes a microfluidic system for performing chemical reactions in droplets. Pet. 5–6 (citing Ex. 1011). And the Petition describes the development of PCR, including microfluidic devices that could perform PCR on a nanoliter scale. *Id.* at 7–8; *see, e.g.*, Ex. 1017 (describing continuous-flow PCR on a chip). According to Petitioner, those microfluidic devices “functioned by injecting a stream of a single PCR reaction mixture into the device, which was then flowed into a microfluidic PCR chamber, where the target sequence was amplified via thermocycling.” Pet. 8 (citing Ex. 1002 ¶ 22).

Despite that background information, we determine that Petitioner has not explained why a person of ordinary skill in the art

would have had a reasonable expectation of success combining Haff's capillary tube PCR system with Quake's microfluidic system to amplify a substrate in droplets. Simply stating that it would have been "routine" is insufficient. To the extent Petitioner relies on the background information to support a reasonable expectation of success, Petitioner fails to explain any connection between the two. For example, if conducting PCR in a *stream* of reaction mixture in a microfluidic device was known, Petitioner has not explained why, with that knowledge, it would have been routine to conduct PCR in *droplets* in a microfluidic device. Moreover, even though Haff describes conducting PCR in a capillary tube device, neither Petitioner nor its declarant explains whether the conditions for conducting PCR in microfluidic droplets would differ, or why a person of ordinary skill in the art would consider conducting PCR in microfluidic droplets to be "routine."

Petitioner contends that a skilled artisan would have had a reasonable expectation of success because Quake teaches how to obtain encapsulated aqueous plugs with a single substrate molecule. Pet. 31. But even with that teaching, Petitioner has not explained why that—or any teaching in Haff or Quake—would establish a reasonable expectation of success in providing conditions that are suitable to amplify a substrate molecule in a microfluidic plug.

The unexplained opinion of Dr. Huck that it would have required no more than routine skill and knowledge in the art "to adapt Haff's device to form a stream of PCR reaction mixture droplets . . . and to conduct PCR amplification, an autocatalytic reaction, in the droplets to amplify the single substrate molecule" (Ex. 1002 ¶ 75) also

is not persuasive. *See* 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (stating a lack of objective support for an expert opinion “may render the testimony of little probative value in [a patentability] determination”).

Without a sufficient explanation regarding the combination of Haff and Quake, we determine that Petitioner has failed to establish a reasonable likelihood that it would prevail in its assertion that claim 1, or dependent claims 2–5, 7–9, and 11, are unpatentable as obvious over Haff and Quake.

D. Obviousness of Claim 6 over Haff, Quake, and Ramsey

Claim 6 depends from claim 1 and further requires that the oil is fluorinated oil. Petitioner argues that claim 6 is unpatentable as obvious over Haff, Quake, and Ramsey. Pet. 46–48. For the same reasons stated above with respect to claim 1, we determine that Petitioner has failed to sufficiently that claim 6 is unpatentable as obvious over the cited references.

III. CONCLUSION

We conclude that Petitioner has not established a reasonable likelihood of prevailing on its assertions that claims 1–9 and 11 of the ’193 patent are unpatentable as obvious.

IV. ORDER

In consideration of the foregoing, it is hereby ordered that the Petition is *denied*.

IPR2015-01163
Patent 8,304,193 B2

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