

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.
Petitioner

v.

BIO-RAD LABORATORIES, INC.
Patent Owner

U.S. Patent No. 9,562,837 to Link
Issue Date: February 7, 2017
Title: Systems For Handling Microfluidic Droplets

Inter Partes Review No. IPR2020-00086

RESPONSIVE DECLARATION OF RICHARD B. FAIR, Ph.D.

TABLE OF CONTENTS

I.	Overview	1
II.	Patent Owner’s Proposed Level Of Ordinary Skill In The Art	3
III.	Patent Owner’s Claim Constructions	6
	A. “separation chamber”	9
	B. “droplet receiving outlet”	10
	C. “coupled”	11
IV.	Patent Owner’s Arguments Regarding Cork Borers	12
V.	Patent Owner’s Arguments Regarding Ismagilov 091	21
VI.	Patent Owner’s Arguments Regarding The Combination of Ismagilov 091 and Quake	27
VII.	Patent Owner’s And The Board’s Reading of Ismagilov 119 And The Combination of Ismagilov 119 and Pamula (Grounds 3a/3b, 4a/4b, 5a/5b)	32
VIII.	Patent Owner’s Assertions Of Secondary Considerations	40
IX.	Conclusion	42

I, Richard B. Fair, hereby declare as follows.

I. OVERVIEW

1. I am over the age of eighteen and otherwise competent to make this declaration. I have been retained as an expert witness on behalf of 10X Genomics, Inc. (“10X Genomics”) for the above-captioned *inter partes* review (“IPR”). I am being compensated for my time in connection with this IPR at my standard legal consulting rate, which is \$600 per hour. I have no personal or financial interest in the outcome of this proceeding.

2. I provided a previous October 25, 2019 declaration in connection with the Petition in this IPR. Ex. 1008 (“Fair Initial Declaration”). Certain section cross-references in that declaration did not populate correctly, and I have prepared a sheet of cross-reference corrections. Ex. 1083. I understand that this correction sheet was provided to Patent Owner Bio-Rad’s counsel before my July 23, 2020 deposition in this IPR.

3. In preparing this Responsive Declaration, I was asked to review Patent Owner’s Preliminary Response to the Petition (Paper 7), the Board’s Institution Decision (Paper 8), Patent Owner’s Response (Paper 26), and the Declaration of Shelley Anna, Ph.D. submitted with Patent Owner’s Response (Ex. 2016), and to respond to certain arguments and statements made in those materials as further detailed below.

4. In preparing this Responsive Declaration (as in my initial Declaration), I have reviewed the 837 patent and considered each of the documents cited herein, in light of general knowledge in the art. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art (*i.e.*, a person of ordinary skill in the field of microfluidic droplet handling) before May 11, 2006.

5. My background and qualifications are set out in my Initial Declaration, along with my understanding of the applicable legal principles. Ex. 1008 (Fair Initial Declaration), ¶¶8-17, 19-46.

6. In formulating my opinions and preparing this Responsive Declaration, in addition to the materials considered in preparing my Initial Declaration (Ex. 1008 (Fair Initial Declaration), ¶¶18 and Attachment B), I have also considered Patent Owner's Preliminary Response to the Petition (Paper 7), the Board's Institution Decision (Paper 8), Patent Owner's Response (Paper 26), the Declaration of Shelley Anna, Ph.D. submitted with Patent Owner's Response (Ex. 2016), and the transcript of Dr. Anna's October 27, 2020 Deposition in this matter (Ex. 1075) as well as all documents and exhibits cited in this Responsive Declaration.

7. The chart below is reproduced from my October 25, 2019 declaration and summarizes the grounds of unpatentability presented in that declaration:

Ground	Basis	Challenged Claims	References	Claim Construction
1	§ 102	1-2, 4, 10-13, 19-20	Ismagilov	Bio-Rad's
2	§ 103	1-2, 4, 7, 9-13, 19-20	Ismagilov and Quake	Bio-Rad's
3a	§ 103	1-4, 7-13, 19-20	Ismagilov 119	10X's
3b	§ 103	1-4, 7-13, 19-20	Ismagilov 119	Bio-Rad's
4a	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 634	10X's
4b	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 634	Bio-Rad's
5a	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 238	10X's
5b	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 238	Bio-Rad's

II. PATENT OWNER'S PROPOSED LEVEL OF ORDINARY SKILL IN THE ART

8. I understand that Bio-Rad proposes a different level of ordinary skill for a person of ordinary skill in the art at the time of the 837 patent than I proposed in my Initial Declaration. I understand Bio-Rad proposes that:

A POSA at the time of the '837 patent would have had at least the equivalent of a Bachelor's degree in engineering, physics, or chemistry and two years of academic, research, or industry experience related to fluid mechanics, fluid dynamics, or microfluidics. Additional training or study could substitute for work experience and additional work experience or training could substitute for formal education.

Patent Owner Response, 17-18. I understand that Dr. Anna proposes the same level of skill in her declaration. Ex. 2016 (Anna Declaration), ¶72. Under this articulation of the level of skill, I was at least a person of ordinary skill (and, indeed, a person of more than ordinary skill) as of the earliest possible priority date of the 837 patent.

9. As I stated in my Initial Declaration:

In my opinion, a person of ordinary skill in the art in the context of the 837 patent as of the earliest possible priority date would have (1) a PhD in chemistry, biochemistry, mechanical or electrical engineering, or a related discipline with one year of experience related to systems for handling microfluidic droplets, (2) a Bachelor of Science in such fields with four years of such experience, or (3) a higher level of education but less relevant practical experience, or more practical experience but less education that would be equivalent to these qualifications before the effective filing date (post-AIA) or before the time of invention (pre-AIA) of the claimed invention. The person of ordinary skill in the art would have knowledge of scientific literature concerning droplets (including emulsions), and systems and methods for handling them (including both their formation and handling downstream of formation), their applications, and chemistry, components, and reactions that occur within them. A person of ordinary skill in the art may have worked on a multidisciplinary team and drawn on his or her own skills along with certain specialized skills of others; and a chemist, engineer, and biologist may have been part of the team. Before the effective filing date or time of invention, the state of the art included the teachings of the references in this Petition. A person of ordinary skill in the art would

have been aware of other important references on handling microfluidic droplets.

Ex. 1008 (Fair Initial Declaration), ¶47.

10. I maintain my opinion that the level of skill I described, including the level of education and/or work experience and the collaboration with a multidisciplinary team, is the correct level of skill of a person of ordinary skill in the art in the context of the 837 patent as of the earliest possible priority date (i.e., in 2006-2007). This is based on my experience working in this field and working with others in this field who consistently had that level of education and/or experience and worked with a multidisciplinary team.

11. In reviewing the Patent Owner's Response and Dr. Anna's Declaration, I note that none of Patent Owner's arguments or Dr. Anna's opinions appear to depend on the differences between these two articulated levels of ordinary skill. Indeed, Dr. Anna states that her opinions are the same under either level of skill. Ex. 2016 (Anna Declaration), ¶74.

12. Based on my review of the Patent Owner's Response and Dr. Anna's Declaration, I also understand that Patent Owner and Dr. Anna do not dispute that "[t]he person of ordinary skill in the art would have knowledge of scientific literature concerning droplets (including emulsions), and systems and methods for handling them (including both their formation and handling downstream of formation), their applications, and chemistry, components, and reactions that occur within them" (Fair

Initial Declaration, ¶47) including, for example, the well-known structures, teachings, and principles that I summarized in my description of the state of the art in my Initial Declaration. Ex. 1008 (Fair Initial Declaration), ¶¶49-59.

13. Even applying Patent Owner's and Dr. Anna's articulation of the level of ordinary skill (should the Board decide to adopt that proposed level of skill), it is still my opinion that the Challenged Claims are anticipated and obvious in view of the Petitioned Grounds for the reasons I explained in my Initial Declaration.

III. PATENT OWNER'S CLAIM CONSTRUCTIONS

14. I understand that the Board indicated in its Institution Decision that the Board intends to apply Bio-Rad's expected claim constructions for "separation chamber" and "droplet receiving outlet" as those expected claim constructions were articulated in the Petition. Institution Decision, 9-17.

15. I also understand that the Patent Owner proposed in its Patent Owner Response claim constructions for three terms: "separation chamber," "droplet receiving outlet," and "coupled." Patent Owner Response, 18-28.

16. I have compared Patent Owner's proposed constructions with the Bio-Rad expected constructions addressed in the Petition and in my Initial Declaration. Ex. 1008 (Fair Initial Declaration), ¶¶77-98. Below, I have reproduced the claim construction table from my Initial Declaration for the terms proposed for construction by Patent Owner and added Patent Owner's proposed constructions:

Claim Term	10X Construction	Bio-Rad Expected Construction	Bio-Rad's POR Construction
<p>“separation chamber”</p> <p>(Claim 1)</p>	<p>“a space that is substantially enclosed”</p>	<p>Broad enough to encompass an open well.</p> <p>(Ex. 1026, 9-13, 16-20)</p>	<p>“chamber sized to accommodate multiple droplets and an immiscible fluid in separated form”</p> <p>(Patent Owner Response, page 18)</p>
<p>“droplet receiving outlet”</p> <p>(Claim 1)</p>	<p><u>Subject to 112(f):</u></p> <p>Structure: the outlet structure described at 3:46-58, 53:21-35, or outlet 805 as described at 54:34-46, and Figure 38 and equivalents thereof</p> <p>Function: receiving substantially only droplets when exiting from the chamber</p> <p>Alternatively, if not subject to 112(f): “a structure connected to the interior space of the chamber and configured so that substantially only droplets flow into it when exiting the chamber”</p>	<p>Broad enough to include the opening at the top of an open outlet well</p> <p>(Ex. 1026, 11-12.)</p>	<p>“portion of the separation chamber where droplets are collected”</p> <p>(Patent Owner Response, page 22)</p>

Claim Term	10X Construction	Bio-Rad Expected Construction	Bio-Rad's POR Construction
“coupled” (Claims 7-8)	“fastened or joined”	Broad enough to encompass transporting by pipette between an alleged outlet/chamber and vessel. (Ex. 1026, 21-22.)	“operably linked” (Patent Owner Response, page 26)

17. In my opinion, Patent Owner's proposed claim constructions in the Patent Owner Response confirm that the Petition and my Initial Declaration properly articulated and applied Patent Owner's understanding of the Challenged Claims. Patent Owner Response, 18-28; Petition, 17-23; Ex. 1008 (Fair Initial Declaration), ¶¶77-98, 103-104, 129, 134, 149-150, 159, 173, 176, 185-186, 188, 190, 193, 205. Patent Owner's proposed claim constructions do include the structures and configurations relied on and described in the Petition and in my Initial Declaration.

18. Whether under Bio-Rad's formally proposed constructions from the Patent Owner Response or under the expected Bio-Rad constructions from the Petition, it remains my opinion that the Petition and my Initial Declaration show that the Challenged Claims are unpatentable in view of:

- Ismagilov's disclosures including a collection well either alone (Ground 1)
or in view of a person of ordinary skill in the art's knowledge as confirmed
by and further in view of Quake (Ground 2), and

- Ismagilov 119’s disclosures including a density sorter in view of a person of ordinary skill in the art’s knowledge (Ground 3b) or further in view of Pamula (Grounds 4b-5b).

See generally Petition; Ex. 1008 (Fair Initial Declaration).

19. It also remains my opinion that, as explained in the Petition and in my Initial Declaration, the Challenged Claims are also unpatentable under 10X’s proposed claim constructions in view of Ismagilov 119’s disclosures including a density sorter in view of a person of ordinary skill in the art’s knowledge (Ground 3a) or further in view of Pamula (Grounds 4a-5a). Ex. 1008 (Fair Initial Declaration), Section XI. Overview of Grounds 1-5, ¶¶100-114.

20. Below I provide some additional explanation for my opinion that Patent Owner’s proposed claim constructions are consistent with the expected Bio-Rad claim constructions and do include the structures and configurations relied on and described in the Petition and in my Initial Declaration.

A. “separation chamber”

21. Patent Owner’s construction of “separation chamber” (Patent Owner Response, 18) as a “chamber sized to accommodate multiple droplets and an immiscible fluid in separated form” is broad enough to include Ismagilov’s open-topped collection well which is sized to accommodate multiple droplets and an

immiscible fluid in separated form. Petition, 35-47; Ex. 1008 (Fair Initial Declaration), ¶¶129-134, 150-154, 160-161, 163-165, 167, 169-170, 172-174, 176.

22. Patent Owner's expert Dr. Anna testified at deposition that substantially enclosed spaces such as the density sorter in Grounds 3b/4b/5b meet Patent Owner's claim construction if sized to accommodate multiple droplets and an immiscible fluid in separated form. Ex. 1075 (Anna Deposition), 145:2-146:1, 148:18-149:16. The Ismagilov 119-based density sorter meets Patent Owner's "sized to accommodate..." construction as I explained in my Initial Declaration and as shown in the Petition. Petition, 56-67; Ex. 1008 (Fair Initial Declaration), ¶¶135-149, 155-159, 162, 166, 168, 171, 175.

B. "droplet receiving outlet"

23. Patent Owner's construction of "droplet receiving outlet" as "portion of the separation chamber where droplets are collected" (Patent Owner Response, 22) is broad enough to include the open top of Ismagilov's collection well where droplets will float to the top of the denser fluorinated oil and collect (and where collection can also be performed by micropipette). Petition, 35-47; Ex. 1008 (Fair Initial Declaration), ¶¶129-134, 150-154, 160-161, 163-165, 167, 169-170, 172-174, 176. Patent Owner's expert Dr. Anna testified at deposition that Patent Owner's construction places no restriction on "how much droplet and how much other

material” is received at the “droplet receiving outlet.” Ex. 1075 (Anna Deposition), 156:4-14, 153:16-160:8.

24. Patent Owner’s expert Dr. Anna testified at deposition that an outlet that receives substantially only droplets such as in the density sorter in Grounds 3b/4b/5b meets Patent Owner’s claim construction. Ex. 1075 (Anna Deposition), 152:1-153:15. The Ismagilov 119-based density sorter includes an outlet portion where droplets are collected as I explained in my Initial Declaration and as shown in the Petition. Petition, 58-64; Ex. 1008 (Fair Initial Declaration), ¶¶135-149, 155-159, 162, 166, 168, 171, 175.

C. “coupled”

25. Patent Owner’s construction of “coupled” in claims 7-9 as “operably linked” (Patent Owner Response, 26) is broad enough to include any operable linkage, including techniques well-known to a person of ordinary skill in the art and rendered obvious by Ismagilov, e.g., using a micropipette or a section of tubing to move droplets from the collection well to another vessel such as a sample tube. Petition, 1-2, 35-36, 47-48; Ex. 1008 (Fair Initial Declaration), ¶¶129-131, 183-188, 191-193.

26. Patent Owner’s expert Dr. Anna testified at deposition that Patent Owner’s construction of “coupled” includes objects that are fastened or joined together so long as the objects “still operate in the manner intended, which is

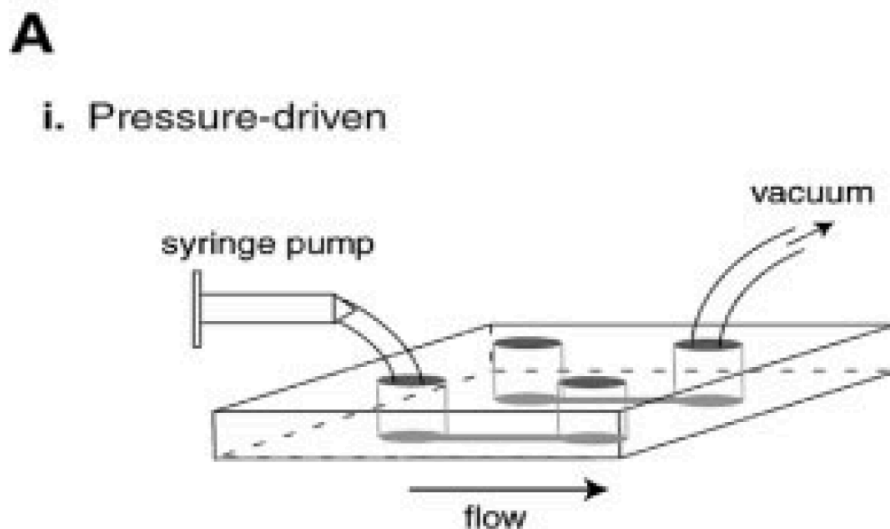
essentially what I mean by operably linked.” Ex. 1075 (Anna Deposition), 161:25-162:6, 160:21-161:24. In Ismagilov’s and Ismagilov 119’s disclosures of adapting the outlet “for receiving ... a segment of tubing or a ... a standard 1.5 ml centrifuge tube” and of collection of droplets/plugs “by micropipette,” the outlet, tubing, sample tube, and micropipette all still operate in the manner intended. Petition, 35-36, 47-48, 58-59, 68-70; Ex. 1008 (Fair Initial Declaration), ¶¶129-131, 183-188, 191-193.

IV. PATENT OWNER’S ARGUMENTS REGARDING CORK BORERS

27. Patent Owner states that Ismagilov’s disclosure of “wells or reservoirs” refers to “commonly known elements of microfluidic devices from the time” of Ismagilov and refers to Ismagilov’s disclosure of using a “cork borer” to cut these vertical wells or reservoirs into the PDMS when preparing the devices. Patent Owner Response, 9. Patent Owner describes cutting such outlet wells using a cork borer as a “standard off-the-shelf technique[] for having droplets flow out of the device that [was] already well known in the art...” Patent Owner Response, 9. Dr. Anna agrees. Ex. 2016 (Anna Declaration), ¶¶35-36. I agree that the use of cork borers to cut vertical well or reservoir structures through the layer of PDMS down to the glass cover floor of the microfluidic chip to create collection wells at outlets was a well-known technique prior to the 837 patent, and Ismagilov discloses this. Ismagilov,

16:35-36; Ex. 1008 (Fair Initial Declaration), ¶¶122, 153, 160-161; *see also* Ismagilov, 16:23-47.

28. Indeed, Patent Owner's Exhibit 2033, a 2003 article by Samuel K. Sia & George M. Whitesides confirms this. Ex. 2033. Both Patent Owner and Dr. Anna describe this 2003 Sia and Whitesides article as describing hole punching techniques that were "common at the time" for the formation of wells. Patent Owner Response, 16-17; Ex. 2016 (Anna Declaration), ¶68. I agree that this article depicts and describes using a cork borer to cut vertical wells at **both** the inlets and the outlets of microfluidic chips and that this was a technique "common at the time" for forming wells such as the collection well disclosed by Ismagilov. For example, Figure 1A of Exhibit 2033 is shown below:



Ex. 2033, 3 (Fig. 1A). This figure shows a PDMS substrate layer with two microchannels (light gray) formed along the bottom of the PDMS layer. Each microchannel is shown with a vertical, cylindrical well cut at the start (inlet) and at

the end (outlet) of the microchannel. A glass cover slip (or another layer of PDMS or other material) will form a flow underneath the PDMS layer (else the fluids would just fall out and would not flow through the channel from inlet to outlet as described). The figure also depicts two options for creating a pressurized flow of fluid through the microchannels—either a syringe pump pushing fluid through from the inlet well or a vacuum pulling from the outlet well (in either case, the well is shown as adapted for receiving a segment of tubing). The article confirms that these wells are cut using a cork borer tool, just as Ismagilov discloses for fabrication of its collection well: “Small holes are drilled into the PDMS using a borer to produce inlets and outlets.” Ex. 2033, 2.

29. Patent Owner and Dr. Anna state that the outlet wells of Exhibit 2033 “were commonly punched using sharpened syringe needles.” Patent Owner Response, 16-17; Ex. 2016 (Anna Declaration), ¶68. However, that is not what Exhibit 2033 says. The word “needle” is not used anywhere in Exhibit 2033. Instead, the article states that a “borer” (that is, a cork borer) is used to produce the inlets and outlets. Ex. 2033, 2. When Dr. Anna was asked about this figure at her deposition, she agreed that the wells shown in Figure 1A of Exhibit 2033 are the type of holes made using a cork borer:

Q. And in this case, what’s being shown is that the hole goes through the PDMS substrate from a top surface down through the level of the channels; is that correct?

A. Well, again, very little detail is given. This is just a schematic so it really doesn't give that much detail.

It appears that I could interpret those as holes going through the PDMS, but I really don't know for sure since it's just a schematic diagram and there's not really any detail in the caption. I'd have to look really through the main body of the text to see if they describe it further. **But that would be a reasonable way to interpret it.**

Q. Are those the type of holes that could be made by a cork borer?

A. Well, I mean, **a cork borer could make holes like that.** I don't know if these were -- well, this is even just a schematic so it's not really -- doesn't really tell me anything about how they were made."

Ex. 1075 (Anna Deposition), 114:9-115:3; *see also* Ex. 1075 (Anna Deposition), 111:10-115:3. The text of the article confirms these wells are made using a cork borer, not a syringe needle. Ex. 2033, 2 ("Small holes are drilled into the PDMS using a borer to produce inlets and outlets.").

30. Dr. Anna states (without citation or further explanation) that "[a] diameter of 1 mm would generally be the same size or larger than the size of a punch hole created by the standard techniques from the timeframe disclosed in Ismagilov using a syringe needle or cork borer." Ex. 2016 (Anna Declaration), ¶132. Dr. Anna and Patent Owner go on to rely on this assertion to argue that a person of ordinary skill in the art would not know how to make a collection well in Ismagilov's system that could accommodate a micropipette tip for collection because available micropipette tips have a diameter of 1 mm (which equals 1000 μm). Patent Owner

Response, 37; Ex. 2016 (Anna Declaration), ¶132. Although I agree that a person of ordinary skill in the art would know that micropipette tips have a diameter of 1 mm, I disagree with Dr. Anna's and Patent Owner's assertion that the well-known technique of creating vertical collection wells at outlets using a cork borer was only used to create wells with a diameter of up to 1 mm.

31. Prior to the 837 patent, cork borers were (and still are today) readily available in diameters of 2 mm, 4 mm, and larger sizes and were (and are) used by persons of ordinary skill in the art to cut vertical collection wells with a diameter of 2 mm and larger. Dr. Anna testified that she did not investigate and does not know what size cork borers were available:

Q. Did cork borers at the time come in sizes other than 1 millimeter?

A. I really don't know. I don't believe that I ever shopped for a cork borer at that time so I don't know what sizes they came in.

Q. So you don't know what sizes cork borers came in?

A. Right. That's what I said.

...

Q. What are all the other sizes of cork borers that you're aware of?

A. I couldn't tell you other sizes that cork borers come in. Like I said, I've never shopped for a cork borer. So I don't know the whole list of sizes you could talk about.

Ex. 1075 (Anna Deposition), 84:24-85:6, 85:25-86:5. References from the time confirm not only that cork borers of 2 mm and 4 mm in diameter were available, but that they were also in use by persons of ordinary skill in the art to cut wells and

reservoirs in PDMS microfluidic substrates. For example, Quake (Ex. 1006) confirms that by 2001 (before Ismagilov, let alone the 837 patent), persons of ordinary skill in the art were already using cork borers to make collection wells of at least 2 mm in diameter in microfluidic elastomer chips including PDMS chips:

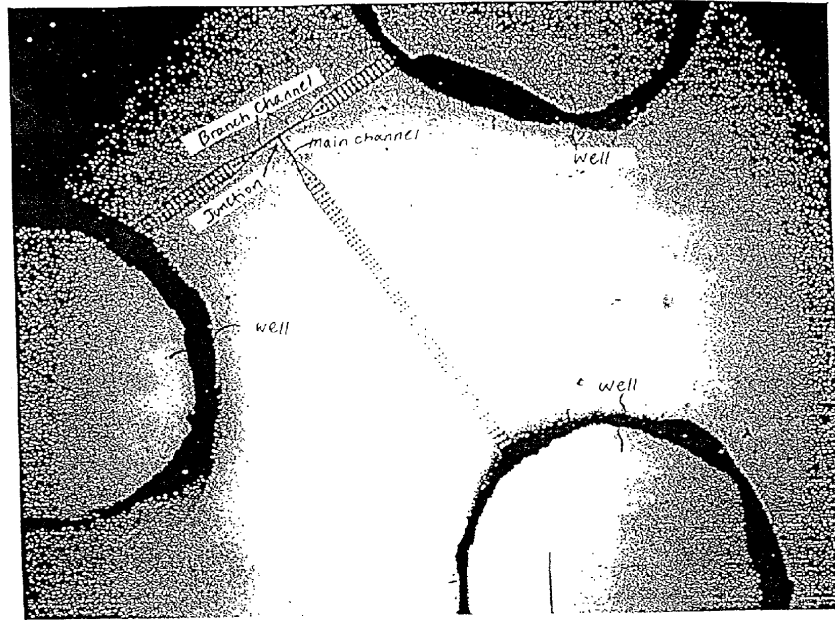


Fig 6

[0196] A representative device of the invention is shown in FIG. 6. The etching process is shown schematically in FIG. 7. Standard micromachining techniques were used to create a negative master mold out of a silicon wafer. The disposable silicone elastomer chip was made by mixing General Electric RTV 615 components (36) together and pouring onto the etched silicon wafer. After curing in an oven for two hours at 80° C., the elastomer was peeled from the wafer and bonded hermetically to a glass cover slip for sorting. . . The device shown has channels that are 100 μm wide at the wells, narrowing to 3 μm at the sorting junction (discrimination region). The channel depth is 4 μm , and

the wells are 2 mm in diameter.

[0197] . . . The inlet well and two collection wells were incorporated into the elastomer chip on three sides of the “T” forming three channels (FIGS. 6 and 7). The chip was adhered to a glass coverslip and mounted onto the microscope. . . .

EXAMPLE 8

Exemplary Embodiment and Additional Parameters

[0215] Microfluidic Chip Fabrication

[0216] In a preferred embodiment, the invention provides a “T” o[r] “Y” shaped series of channels molded into optically transparent silicone rubber or PolyDiMethylSiloxane (PDMS), **preferably PDMS**. This is cast from a mold made by etching the negative image of these channels into the same type of crystalline silicon wafer used in semiconductor fabrication. As described above, the same techniques for patterning semiconductor features are used to form the pattern of the channels. **The uncured liquid silicone rubber is poured onto these molds placed in the bottom of a Petri dish.** To speed the curing, these poured molds are baked. After the PDMS has cured, it is removed from on top of the mold and trimmed. **In a chip with one set of channels forming a “T”, three holes are cut into the silicone rubber at the ends of the “T”, for example using a hole cutter similar to that used for cutting holes in cork, and sometimes called** **cork borers. These holes form the sample, waste and collection wells in the completed device.** . . . The device is then placed onto a No. 1 (150 μm thick) (25x25 mm) square microscope cover slip. The cover slip forms the floor (or the roof) for all three channels and wells. The chip has a detection region as described above.

Ex. 1006 (Quake), Fig. 6, ¶¶196-197, 216; *see also* Ex. 1006 (Quake), ¶¶192-198, 215-216. A 2005 article by Sia and Whitesides (and others)—the same two authors of the Exhibit 2033 article that Patent Owner and Dr. Anna identified and relied on as disclosing common techniques—discloses the use of cork borers of 4 mm in diameter to cut reservoir holes in PDMS in microfluidic chips:

Microfluidic channels with square, rectangular, and semicircular cross sections in PDMS were fabricated using soft lithography. Inlet/outlet holes were drilled into the PDMS layer, and the channels were bonded to glass irreversibly. For a single valve, **we used a cork borer to drill a hole (~4 mm in diameter) in the PDMS layer** directly above a channel, as a reservoir for the urethane; the depth varied, but was typically ~ 2 mm...

Ex. 1076 (2005 article by Sia, Whitesides, et. al. in *Analytical Chemistry*, titled *Torque-Actuated Valves for Microfluidics*), 5. Sia and Whitesides confirmed that they used commercially available cork borers from McMaster-Carr Inc.: “Materials... cork borers from McMaster-Carr Inc.” Ex. 1076, 2.

32. Cork borers commercially available today from McMaster-Carr Inc. and others similarly come in sizes of 2 mm in diameter, 4 mm in diameter, and larger diameters. For example, today McMaster-Carr offers a set of six hand-driven cork borers in sizes ranging from 3/16” up to 1/2” (or 4.7625 mm to 12.7 mm) in diameter and offers a hammer-driven set in sizes ranging from 2 mm up to 50 mm in diameter. Ex. 1077 (McMaster-Carr website captures), 1-2, 3, 8. Fisher Scientific, a division

of well-known laboratory equipment provider Thermo Fisher Scientific, similarly offers a set of hand-driven cork borers in sizes ranging from 4.8 mm to 16.7 mm in diameter. Ex. 1078 (Fisher Scientific website capture), 1. Sigma-Aldrich (another well-known supplier of laboratory equipment) similarly offers a set of hand-driven cork borers in sizes ranging from 3/16" up to 1/2" (or 4.7625 mm to 12.7 mm) in diameter. Ex. 1079 (Sigma-Aldrich website capture). Although these websites are from today, they are consistent with my experience of cork borers that were available in and around 2006-2007 prior to the 837 patent, and they are consistent with what the above references from that time describe using. Indeed, I do not recall being able to find cork borers with a diameter of less than 2 mm in the 2006-2007 timeframe.

33. In view of the above and as I explained in my Initial Declaration, a person of ordinary skill in the art reading Ismagilov as a whole would understand Ismagilov's teachings that (i) the collection well at the outlet can be cut vertically through the PDMS layer using a cork borer and (ii) collection from that well "can also be done using micropipettes," disclose cutting a vertical collection well through the PDMS layer at the microchannel outlet with a diameter large enough to accommodate the tip of a micropipette, that is, a diameter of at least 2 mm and certainly greater than the 1 mm diameter of the micropipette tip. Ex. 1008 (Fair Initial Declaration), ¶¶129-134, 160-161, 167, 170.

V. PATENT OWNER’S ARGUMENTS REGARDING ISMAGILOV 091

34. Patent Owner asserts in its Patent Owner Response (and Dr. Anna states as well) that “[t]here is simply no disclosure in Ismagilov that teaches any chamber with the dimensions and configuration claimed in the ‘837 patent...” Patent Owner Response, 34; Ex. 2016 (Anna Declaration), ¶133; *see also* Patent Owner Response, 38-39, 42, 50 (similar assertions regarding purportedly “no disclosure” in Ismagilov); Ex. 2016 (Anna Declaration), ¶¶140, 146 (similar assertions regarding purportedly “no disclosure” in Ismagilov). I disagree for the reasons already explained in my Initial Declaration (for example, Ex. 1008 (Fair Initial Declaration), ¶¶121-123, 160-161) and as further explained below.

35. Ismagilov discloses that its outlet: “collects” plugs/droplets, is in fluid communication with a “well or reservoir”, that plugs/droplets are moved to the appropriate outlet, that “collection” at the outlet “can also be done using micropipettes”, and that the outlet “can be adapted for receiving . . . a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube.” Ismagilov, 9:5-8, 14:36-40, 17:18-30; Ex. 1008 (Fair Initial Declaration), ¶¶160-161, 167, 170, 173-174; Petition, 35-37. The use of the words “well” and “reservoir” which a person of ordinary skill in the art would understand to be vertical, bucket-shaped storage areas; that the outlet port “collects ... plugs” (plural) and that “plugs” (plural) are moved to the outlet; and the teaching that collection from the outlet can be done “using

micropipettes” all confirm that a person of ordinary skill in the art reading Ismagilov’s teachings of a collection well/reservoir at the outlet as a whole would understand Ismagilov expressly discloses a “chamber sized to accommodate multiple droplets and an immiscible fluid in separated form” including a “portion ... where droplets are collected” as Patent Owner applies those claim constructions. Ex. 1008 (Fair Initial Declaration), ¶¶129-134, 160-161, 167, 170; Petition, 35-37, 40-41, 44-45.

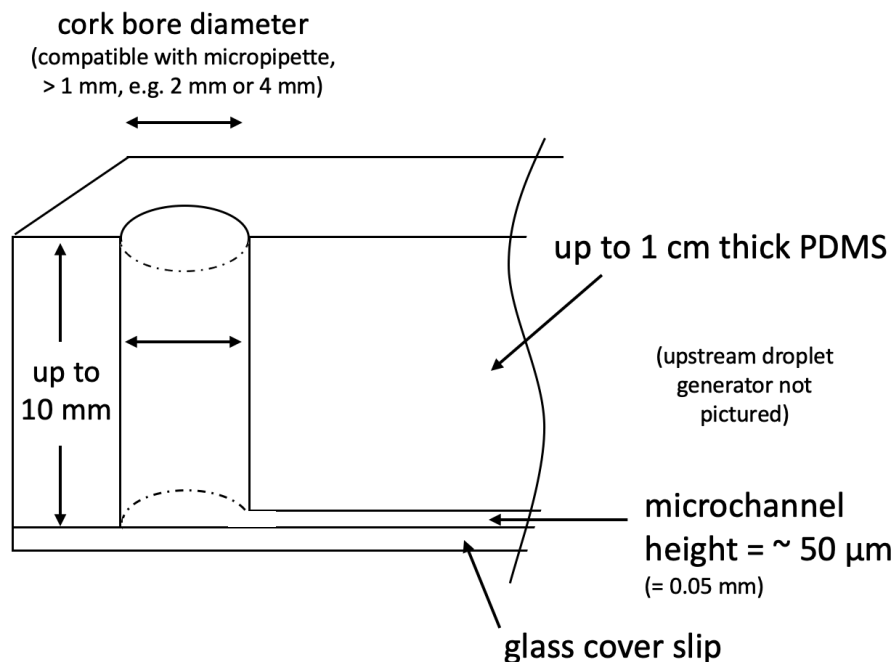
36. Ismagilov also provides additional details for forming the microfluidic substrate chips, and these teachings further confirm the shape, size, and orientation of the collection well/reservoir. Ex. 1008 (Fair Initial Declaration), ¶¶120-123, 160; Petition, 31-32, 40-41. The microchannels are formed on the bottom of a PDMS layer using a mold formed “by etching the negative image of these channels” into a silicon wafer and pouring uncured PDMS onto the wafer inside a Petri dish. Ismagilov, 16:23-32; Ex. 1008 (Fair Initial Declaration), ¶¶120-123, 160. The thickness of the PDMS is up to “about 1 cm.” similar to the depth of a Petri dish. *See* Ismagilov, 16:42-47; Ex. 1008 (Fair Initial Declaration), ¶¶120-123, 160. A thickness of about 1 cm for the PDMS layer is wholly consistent with the use of a Petri dish as the container for the uncured PDMS, as Petri dishes range in depth from about 1-2.5 cm (10 mm to 25 mm). Ex. 1080 (Sigma-Aldrich website capture offering Petri dishes with depths/heights ranging from 10mm to 25 mm); Ex. 1081

(Fischer Scientific website capture offering Petri dishes with depths/heights ranging from 10 mm to 25 mm).

37. Ismagilov teaches that after the PDMS is cured, holes such as the collection well/reservoir can then be cut vertically through the PDMS down to the microchannels at the bottom of the PDMS layer using “a tool such as a cork borer.” Ismagilov 16:36-36; Ex. 1008 (Fair Initial Declaration), ¶¶120-123, 160. The PDMS layer is then placed (channels side down) onto a glass microscope slide cover slip or other flat surface which forms the floor of the channels and the collection well. Ismagilov 16:38-41; Ex. 1008 (Fair Initial Declaration), ¶¶120-123, 160; Petition, 31-32, 40-41. Thus a person of ordinary skill in the art reading Ismagilov as a whole would understand Ismagilov discloses a collection well/reservoir cut vertically through an up to 1 cm/10 mm thick layer of PDMS using a cork borer with a diameter sufficient to allow collection by micropipette (i.e., > 1 mm, such as the 2 mm or 4 mm diameter cork borers discussed above). Ex. 1008 (Fair Initial Declaration), ¶¶120-123, 160. The horizontal microchannels of Ismagilov are repeatedly shown and described as having a diameter on the order of 28-60 micrometers (~1/20th of 1 mm) or less. *E.g.*, Ismagilov, Figs. 7A-7C, 26A, 27B, 30, 15:24-40, 22:43-44, 41:14-17. Although Ismagilov does also disclose that “[t]he size of channels may be increased to about 500 μ m (corresponding to a volume of about 250 nL) or more” (Ismagilov, 19:64-66), none of the figures or example systems described by

Ismagilov use channels that large. In addition, even a microchannel with a diameter of 500 μm (or 0.5 mm) would still have a smaller cross section than Ismagilov's disclosed collection well which has a diameter large enough to accommodate a micropipette (i.e., > 1 mm, such as the 2 mm or 4 mm diameter cork borers discussed above). Based on Ismagilov's teachings, I have prepared an illustrative diagram of a vertical cross section of Ismagilov's disclosed collection well:

Ismagilov's Collection Well (Illustrative)



As I explained in my Initial Declaration, a person of ordinary skill in the art would understand this to be the collection well structure expressly disclosed by Ismagilov. Ex. 1008 (Fair Initial Declaration), ¶¶120-123, 130-131, 160-161, 167, 170, 173-174. This structure would be familiar to a person of ordinary skill in the art (such

vertical collection well structures were well-known in the art). Ex. 1008 (Fair Initial Declaration), ¶¶130-131, 160-161.

38. A person of ordinary skill reading Ismagilov as a whole would also know that the well must extend upright and out of the plane from the microchannel because a person of ordinary skill in the art would know that using a cork borer to cut a well within the same plane as the microchannel (i.e., a well with the same height as the microchannel) would be incompatible with Ismagilov's system and teachings. Patent Owner and Dr. Anna agree that Ismagilov discloses that its wells are formed using a cork borer to cut through the entire PDMS layer. Section IV. (above); Patent Owner Response, 9; Ex. 2016 (Anna Declaration), ¶¶35-36. In Ismagilov's system, cutting a well with the same height as the microchannel would thus mean the microchannel height also extends through the entire PDMS layer, leaving the microchannel open at the top. Ismagilov, 16:23-41. Because Ismagilov uses "pressure-driven" flows of fluids in the microchannels to generate plugs/droplets, a person of ordinary skill in the art would know the microchannels cannot be open at the top, else applying pressure would spill fluids out the tops of the channels and make the system inoperable. For example, Ismagilov is titled "Device and Method for Pressure-Driven Plug Transport and Reaction" and discloses:

SUMMARY ACCORDING TO THE INVENTION

In accordance with the invention, a method of conducting a reaction within a substrate is provided that comprises introducing a carrier-fluid into a first channel of the substrate; introducing at least two different plug-fluids into the first channel; **and applying pressure to the first channel to induce a fluid flow in the substrate to form substantially identical plugs** comprising a mixture of plug-fluids.

Ismagilov, 2:50-58;

Channels and Devices

In one aspect of the invention, a device is provided that includes one or more substrates comprising a first channel comprising an inlet separated from an outlet; optionally, one or more secondary channels (or branch channels) in fluid communication with the first channel, at least one carrier-fluid reservoir in fluid communication with the first channel, at least two plug-fluid reservoirs in fluid communication with the first channel, **and a means for applying continuous pressure to a fluid within the substrate.**

Ismagilov, 14:19-29; Ex. 1008 (Fair Initial Declaration), ¶132; Petition, 37, 43.

Ismagilov does state in describing the word “channel” that:

The term “channel” refers to a conduit that is typically enclosed, although it may be at least partially open, and that allows the passage through it of one or more types of substances or mixtures, which may be homogeneous or heterogeneous, including compounds, solvents, solutions, emulsions, or dispersions, any one of which may be in the solid, liquid, or gaseous phase.

Ismagilov, 7:34-40. Reading this in the context of Ismagilov as a whole, a person of

ordinary skill in the art would understand that this reference to “partially open” channels refers to the inlets and outlets of the channels where the inlet/outlet wells are cut (for example, the open collection well at the end of the microchannel depicted in the cross-section illustration above) which is what “allows the passage through [the channel] of one or more types of substances or mixtures”. This is confirmed by Ismagilov’s disclosures that the microchannels where the plugs/droplets are formed are under continuous pressure and therefore must be enclosed other than where the fluid is introduced and exits. Ismagilov’s disclosure of forming plugs/droplets in the microchannel using pressure-driven flow confirms that there must be a layer of PDMS above the microchannels and Ismagilov’s disclosure of forming collection wells by cutting vertically through the entire PDMS layer using a cork borer discloses that the collection well will extend upright and out of the plane of the microchannels through the layer of PDMS above the microchannels.

VI. PATENT OWNER’S ARGUMENTS REGARDING THE COMBINATION OF ISMAGILOV 091 AND QUAKE

39. Patent Owner and Dr. Anna assert that the Petition and my Initial Declaration did not identify “a sufficient motivation to combine Ismagilov and Quake, which are directed to two entirely different types of systems.” Patent Owner Response, 45; Ex. 2016 (Anna Declaration), ¶158. I disagree. My Initial Declaration and the Petition identify and explain how and why a person of ordinary skill in the art would be motivated to combine Ismagilov and Quake, and Ismagilov and Quake

in fact describe very similar types of systems including the same PDMS microfluidic chip fabrication techniques and the use of cork borers to cut vertical collection wells at microchannel outlets. Ex. 1008 (Fair Initial Declaration), ¶¶59, 104-107, 150¹-154, 163-165, 172, 176, 186; Petition, 11-12, 14-15, 23-28, 38-42, 45-48. I understand that the Board stated in its Institution Decision that the Petition explains “how and why a POSA would have combined” Ismagilov and Quake, and “that Quake provides additional details” of the collection well disclosed by Ismagilov, including “explicit disclosure of structural and functional details, such as the relative dimensions of wells and channels.” Institution Decision, 40-41.

40. Based on my review of Patent Owner’s Response and Dr. Anna’s declaration, Patent Owner does not appear to dispute that Quake and Ismagilov disclose the same fabrication techniques for their microfluidic chips (including use of the same PDMS channel molding, cork borers, and glass cover slips), leading to a reasonable expectation of success for the combination of their teachings. Ismagilov, 16:1-47; Quake, ¶¶196, 200, 216; Ex. 1008 (Fair Initial Declaration), ¶¶6, 122-123, 153-154, 165; Petition, 31-32, 42. Patent Owner also does not appear to dispute that Quake teaches forming a “collection well” that has a 2 mm diameter, a volume of at least 30 µl (and thus a height of at least 9.5 mm) by cutting vertically

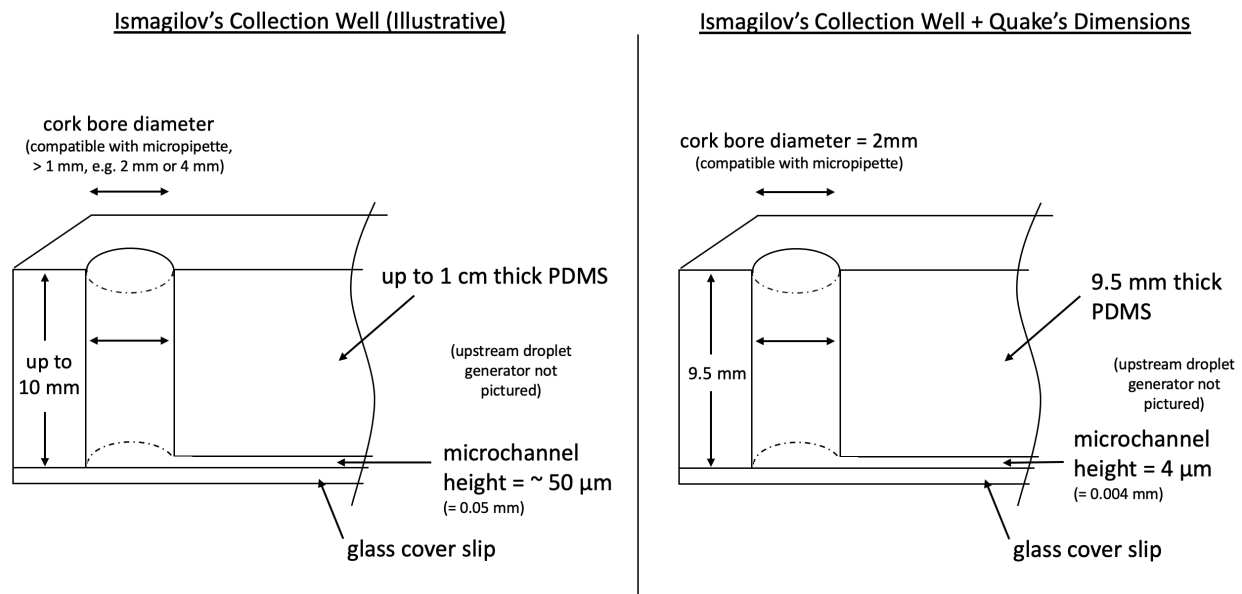
¹ Paragraph 150 of my Initial Declaration contains one of the cross reference cites which I corrected in Exhibit 1083.

through the layer of PDMS using a cork borer. Quake, Figs. 6-8, ¶¶196, 200, 216; Fair, ¶¶153-154, 164-165; Petition, 42.

41. Combining Quake's disclosures of these specific collection well dimensions with Ismagilov's collection well disclosures (including forming a well at the outlet from which collection of plugs/droplets can be performed by micropipette) and the commercial availability of cork borers of 2 mm (and larger) in diameter, as described in my Initial Declaration and as further described in this Responsive Declaration, it would have been obvious to a person of ordinary skill in the art to create in Ismagilov's system a collection well that is 2 mm in diameter cut vertically using a cork borer at the microchannel outlet and having a volume of at least 30 μ l and a height of ~9.5-10 mm. Quake, Figs. 6-8, ¶¶196, 200, 216; Fair, ¶¶153-154, 164-165; Petition 42. At a minimum, a person of ordinary skill in the art reading Ismagilov's disclosure that collection from the outlet collection well can also be done by micropipette would be motivated to look to work by other well-known researchers in the field of microfluidic droplet generation and manipulation (including Quake) and would find it obvious to try Quake's disclosed collection well structure and dimensions since Quake's fabrication techniques match Ismagilov's and Quake's dimensions would accommodate collection by micropipette.

42. Thus, as described in my Initial Declaration, the Petition, and further in this Responsive Declaration, it would be obvious for a person of ordinary skill in the

art reading Ismagilov in view of both the knowledge of a one of ordinary skill and the teachings of Quake to arrive at a collection well that is at least 2 mm in diameter cut vertically using a cork borer at the microchannel outlet and having a volume of at least 30 μl and a height of ~ 9.5 -10 mm. Ex. 1008 (Fair Initial Declaration), ¶¶59, 104-107, 150-154, 163-165, 172, 176, 186; Petition, 11-12, 14-15, 23-28, 38-42, 45-48. The cross section view of Quake's disclosed structure is both very similar to and compatible with the dimensions, structure, and orientation that a person of ordinary skill in the art would understand Ismagilov's teachings to disclose for the collection well, and I have prepared an illustration of that comparison:



43. Patent Owner and Dr. Anna also assert that Ismagilov and Quake “relate to two completely different structures and assemblies with two completely different intended uses.” Patent Owner Response, 46; Ex. 2016 (Anna Declaration), ¶161. I disagree. Quake, like Ismagilov, is a reference regarding “microfluidic

devices and methods” including particularly devices “designed to compartmentalize small droplets of aqueous solution within microfluidic channels filled with oil” in addition to teachings on droplet handling and other subsequent sorting, use, and manipulation of droplets, including specifically “collection wells.” Ex. 1008 (Fair Initial Declaration), ¶¶73, 104-107, 151-154; Quake, ¶¶3-4, 93, 95, 195-200, 213-214, 216, 240-241.

44. Patent Owner appears to argue that because Quake’s Figure 6 and related descriptions describe a microfluidic structure for sorting, a person of ordinary skill in the art would ignore Quake’s teachings regarding that structure. I disagree. Quake discloses that the sorting of cells, viruses/virions, or other particles is an important application of Quake’s droplet generation devices and teaches including a “detection region” downstream of the “droplet extrusion region” and “[i]n sorter embodiments ... a discrimination region, which is downstream from the detection region ... adapted to direct droplets through the discrimination region and into a branch channel.” Quake, *e.g.*, ¶¶12-22, 58-59, 85. Although Quake’s experiments testing the device depicted in Figures 6-8 (and described in Examples 7 and 8) sorted fluorescent beads and cells, Quake discloses that the device can be “a component of an integrated microanalytical chip, in sorting cells or biological materials,” *i.e.*, as the “T-shape ... branch point” of the discrimination region and branch channel. Quake, ¶¶193, 85. Quake similarly discloses that related Example 8’s T-shaped

branch can be used to sort water-in-oil droplets. Quake, ¶¶215-218, 241. These teachings from Quake are directly analogous to Ismagilov's collection well disclosures (*e.g.*, Ismagilov, 17:18-30) and would certainly be read and considered by a person of ordinary skill in the art looking for details about implementing Ismagilov's collection well and turning to Quake as a reference from a well-known researcher in the art.

45. A person of ordinary skill in the art in search of details for implementing Ismagilov's collection well would look to the well-known work of Quake including Figures 6-7, Examples 7-8, and Quake's express teachings of the shape and dimension of "collection wells"—details which I understand Patent Owner to argue a person of ordinary skill in the art would not recognize from Ismagilov's disclosures alone. Quake, ¶¶196-197, 200, 213-214, 216, 240-241 (all describing "collection well[s]"); Ex. 1008 (Fair Initial Declaration), ¶¶104-107, 130-131, 150-154, 163-165; Petition, 25-28, 38-42.

**VII. PATENT OWNER'S AND THE BOARD'S READING OF
ISMAGILOV 119 AND THE COMBINATION OF ISMAGILOV 119
AND PAMULA (GROUNDS 3A/3B, 4A/4B, 5A/5B)**

46. I have reviewed the Institution Decision's analysis of Ismagilov 119, Pamula, and Grounds 3a/3b-5a/5b (as well as Patent Owner's Response and Patent Owner's Preliminary Response regarding these Grounds). Respectfully, it is my opinion that this Board and Patent Owner misread Ismagilov 119's disclosure at

paragraph 123 of sorting plugs/droplets “by their density relative to that of the carrier fluid” in connection with Grounds 3a/3b-5a/5b and misunderstand the combination of Ismagilov 119 and Pamula described in my Initial Declaration and the Petition in connection with Grounds 4a/4b-5a/5b. Ex. 1008 (Fair Initial Declaration), ¶¶102, 108-114, 135-149, 155-159, 162, 166, 168, 171, 175, 178, 179-180, 182, 184-185, 187-188, 190, 192-205, 208, 211; Petition, 56-71; *see also* Institution Decision (Paper 8), 46-47; Patent Owner Response, 59-60.

47. Ismagilov 119, paragraph 123 is reproduced below:

[0123] Plugs can be sorted. For example, the plugs can also be sorted according to their sizes. Alternately, the plugs can be sorted by their density relative to that of the carrier fluid. Alternately, plugs can also be sorted by applying a magnetic field if one group of the plugs contains magnetic materials such as iron or cobalt nanoparticles or ferrofluid.

Ex. 1005 (Ismagilov 119), ¶123. This paragraph describes three examples of how plugs (droplets) can be sorted. The first example refers to sorting of “plugs” (plural) “according to their sizes” (plural)—clearly disclosing the sorting of plugs/droplets from other plugs/droplets based on the multiple (plural) different sizes of the plugs/droplets. Similarly, the third example refers to the sorting of “plugs” “by applying a magnetic field if one group of the plugs contains magnetic materials such as iron or cobalt nanoparticles or ferrofluid”—again, disclosing the sorting of

plugs/droplets from other plugs/droplets based on a characteristic that differs between different groups of plugs (that is, some plugs/droplets contain magnetic materials and some do not). The second example, however, is distinct from the first and third examples. The second example explains that “plugs” (plural) “can be sorted by their density” (singular) “relative to that of the carrier fluid” (“that” meaning relative to the density, singular, of the carrier fluid). This is still an example of sorting plugs/droplets, but this second example is a disclosure of sorting droplets/plugs relative to the carrier fluid rather than relative to other plugs/droplets (since it lacks any discussion of different plural densities among different plugs or groups of plugs). This also makes sense in the context of Ismagilov 119 as a whole—all of the plugs/droplets are aqueous droplets (that is, water droplets) and so will have the same density. Ex. 1008 (Fair Initial Declaration), ¶136; *see also* Ex. 1008 (Fair Initial Declaration) ¶¶137-149.

48. I understand that the Board (at least preliminarily in its Institution Decision) and Patent Owner both disagree, reading Ismagilov 119 paragraph 123’s second example as still being a discussion of sorting plugs/droplets from other plugs/droplets based on different densities of the plugs/droplets. *See* Institution Decision (Paper 8), 46-47; Patent Owner Response, 59-60.

49. However, even under the reading of Ismagilov 119 paragraph 123 where the sorting based on density is a sorting of plugs/droplets relative to other

plugs/droplets, the density sorter structure described in my Initial Declaration and the Petition would still be obvious to a person of ordinary skill in the art. *See* Ex. 1008 (Fair Initial Declaration) ¶¶137-149.

50. Regardless of whether the Ismagilov 119 paragraph 123 disclosure is read as sorting plugs/droplets from oil or sorting plugs/droplets from other plugs/droplets based on density differences, a person of ordinary skill in the art would still recognize the need for a structure where that sorting could take place and would arrive at the density sorter of Grounds 3a/3b-5a/5b. This is not a backwards-looking or hindsight-driven conclusion; rather, it is a result of a person of ordinary skill's knowledge that:

- (i) density-based sorting (whether droplets from oil or droplets from other droplets) relies on the force of gravity which acts vertically;
- (ii) any density-based sorting requires time (especially true for sorting of droplets from other droplets because they may have only small density differences), and space for the droplets to move through the oil, and so to give that process adequate time multiple droplets would be pooled in the vertical chamber; and
- (iii) sorting is pointless without collection of the desired "sorted" result, and because droplets have a different density than the oil (Ismagilov 119, ¶123), they separate from the oil at the top or bottom of the chamber.

Ex. 1008 (Fair Initial Declaration), ¶¶54-57, 102, 108-114, 135-149, 155-159; Petition, 56-71. As my original declaration stated, generally, “[t]he rate of creaming of noninteracting particles depends on density differences and the square of the droplet radius,” and emulsions placed in a relatively large volume will separate. Ex. 1008 (Fair Initial Declaration), ¶¶54-57; Ex. 1009 at 115. Particularly if density differences are relatively small to distinguish two types of droplets, pooling multiple droplets can mean needing to stop the system to allow the droplets time to separate. I understand that neither Patent Owner nor Dr. Anna disagree with my discussion in the summary of the state of the art in my Initial Declaration that “[t]he natural property that fluids of different densities—including droplets—will separate was also well-known, as were the features of containers in which it occurred,” “[i]f a density difference exists between the dispersed and continuous phases, dispersed droplets experience a **vertical force** in a gravitational field,” and that density separation of droplets was already known to be useful, including that “‘the creamed [density separated] droplets can be removed from the initial emulsion and redispersed’ in a large vessel as part of a process of producing monodisperse emulsions.” Ex. 1008 (Fair Initial Declaration), ¶¶54-57.

51. These well-known facts would motivate a person of ordinary skill in the art reading Ismagilov 119’s disclosure to arrive at the described density sorter structure based on Ismagilov 119 and a person of ordinary skill in the art’s

knowledge (Grounds 3a/3b) or Ismagilov 119 and a person of ordinary skill in the art's knowledge in further view of Pamula (Grounds 4a/4b-5a/5b) based on the same explanation, reasoning, and disclosures identified in my Initial Declaration and the Petition. Ex. 1008 (Fair Initial Declaration), ¶¶54-57, 102, 108-114, 135-149, 155-159; Petition, 56-71.

52. If additional structural information is required for either density-based sorting, a person of ordinary skill in the art would have been motivated to look to Pamula for the structure of a device that operated based on the droplet/oil density difference, and nothing precludes using Pamula's waste and collection wells for droplets. Petition, 29-30, 60-64; Fair, ¶¶113-114, 155-158. Ismagilov 119 (Grounds 3a/3b) and Ismagilov 119+Pamula (Grounds 4a/4b-5a/5b) render the claims obvious under either party's constructions (Section III).

53. Restating the explanation from my Initial Declaration briefly here (*see* Ex. 1008 (Fair Initial Declaration), ¶¶54-57, 102, 108-114, 135-149, 155-159), a person of ordinary skill in the art would recognize the need for a structure where Ismagilov 119's density-based sorting could take place (even if paragraph 123 is read as teaching sorting droplets from other droplets based on density). Because density-based separation forces act in the vertical dimension due to gravity, that structure would need to allow for the droplets being sorted to move past each other in the vertical dimension. That rules out the use of Ismagilov's 119 microchannels

themselves as the density sorting structure because the Ismagilov 119 microchannels are consistently described and depicted as constraining the droplets single-file as the droplets fill the dimensions of the channel (and so, droplets could not vertically be sorted from one another within the microchannel based on density). Other forms of sorting of droplets (such as the application of a magnetic field in the horizontal plane) could allow for the sorting of droplets within the channels which are formed in a horizontal plane (e.g., by attracting droplets containing magnetic materials to move to the right at a microchannel junction while non-magnetic droplets would continue along a different channel because they would not be attracted by the magnetic field), but density-based sorting requires the vertical separation chamber described for Grounds 3a/3b-5a/5b. And, because a person of ordinary skill in the art would understand that sorting the droplets based on density would be pointless without a way to collect the desired droplets (e.g., to collect the “crystaliz[ed] proteins, biomolecules, complexes of biomolecules with bound ligand, etc.” disclosed by Ismagilov 119, ¶8), that vertical density sorter structure would need an outlet where the desired droplets (whether more dense or less dense) could be collected.

54. As described in my Initial Declaration, Pamula’s teachings confirm and provide any necessary details to arrive at the same density sorter structure. Ex. 1008 (Fair Initial Declaration), ¶¶54-57, 102, 108-114, 135-149, 155-159. My Initial

Declaration also explains why a person of ordinary skill in the art with Ismagilov's disclosure of sorting plugs/droplets based on density would look to Pamula for disclosures of the details of a structure for performing that density-based sorting, including because the work of my lab group (including the work described in Pamula) was well-known in the field specifically for teachings regarding techniques for droplet handling and was cited together with work by Dr. Ismagilov in review articles summarizing the state of the art at the time. Ex. 1008 (Fair Initial Declaration), ¶¶112-114, 155-156. My Initial Declaration also explains why a person of ordinary skill in the art would have had a reasonable expectation of success in making the described combination in view of the teachings of Ismagilov 119 and Pamula, including because Pamula expressly teaches that channel-based, continuous flow elements like Ismagilov's droplet generator system can be integrated with the Pamula density-sorter system and because the constraining of the movement of droplets via physical channels (as in Ismagilov) or via electric fields that effectively form electromagnetic channels (as in Pamula) were two known and well-understood alternative approaches for manipulating droplets once the droplets are generated. Ex. 1008 (Fair Initial Declaration), ¶¶155-158.

55. And as I explained in this Responsive Declaration above in connection with Patent Owner's proposed claim constructions from the Patent Owner Response, those claim constructions confirm that 10X's proposed claim constructions are a

narrower subset of Patent Owner's constructions/applications of the claim terms and the "separation chamber," "droplet receiving outlet," "coupled," and other claim elements identified for the density sorter of Grounds 3a/3b-5a/5b would also meet Patent Owner's constructions and render obvious the Challenged Claims. Section III. (above); Ex. 1008 (Fair Initial Declaration), ¶¶159, 188.

VIII. PATENT OWNER'S ASSERTIONS OF SECONDARY CONSIDERATIONS

56. I understand that the Board found in its Institution Decision that the secondary considerations assertions made by Patent Owner in Patent Owner's Preliminary Response failed to show the nexus to the Challenged Claims that I understand to be required by the applicable legal standards. Institution Decision, 41-43. Based on my reading of the Patent Owner Response and Dr. Anna's Declaration, Patent Owner and Dr. Anna appear to repeat assertions identical to those raised in Patent Owner's Preliminary Response nearly verbatim (although with slight re-ordering) without any showing of nexus. *Compare* Patent Owner Preliminary Response (Paper 7), 27-34, *with* Patent Owner Response, 53-59. I also understand that Dr. Anna testified at deposition that she was not asked to analyze, did not analyze, and does not know whether the many features of the Bio-Rad and 10X products unrelated to the 837 patent led to their success, praise, or meeting of any unmet need. Ex. 1075 (Anna Deposition), 168:7-204:16. Dr. Anna also testified that she was not asked to analyze, did not analyze, and does not know whether assets

unrelated to the 837 patent led to Bio-Rad's acquisition of RainDance. Ex. 1075 (Anna Deposition), 168:7-204:16.

57. I understand that the International Trade Commission determined the success of 10X's products, praise for 10X's products, and any unmet needs met by 10X's products have a nexus to 10X's own patents, not to Bio-Rad's 837 patent. Ex. 1084 (Initial Determination by International Trade Commission Administrative Law Judge), 51-57, 74; Ex. 1085 (Final Decision by the International Trade Commission), 24-25 (affirming the Initial Determination as to the secondary considerations analysis). I also understand that the Bio-Rad ddSEQ product that Patent Owner asserts practices the 837 patent has been a failure Ex. 1086 (Appellate Briefing and Excerpted Appendix Exhibits from Prior 10X/Bio-Rad 152 Case), 29 (showing poor sales of, poor performance of, and lack of customer satisfaction with Bio-Rad's ddSEQ product).

58. Based on my review of the materials in this matter including Bio-Rad's assertions, I did not identify nor did I see Bio-Rad identify any evidence establishing a nexus between the Challenged Claims and: the commercial success of any product; any evidence that the alleged invention claimed met a long-felt but unmet need; any industry praise or skepticism; any licensing. Nor did I identify nor did I see Bio-Rad identify that others tried and failed to arrive at the alleged inventions. To the contrary, multiple groups had already shown droplet generation and had identified the

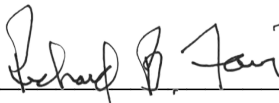
principle of density separation as beneficial, as I describe above and in my Initial Declaration. There is also no evidence of unexpected results, nor would I expect there to be any when the 837 patent focuses on the long-known and well-understood natural principle of separating fluids of different densities.

IX. CONCLUSION

59. It remains my opinion, as an expert in the field of microfluidic droplet handling, that the 837 patent claims are unpatentable. All elements recited in claims 1-2, 4, 10-13, and 19-20 are anticipated by the prior art, as discussed above and in connection with Ground 1 in my Initial Declaration. Further, a person of ordinary skill in the art would have been motivated to combine the art cited in Grounds 2-5b to arrive at claims 1-4, 7-13, and 19-20 of the 837 patent with a reasonable expectation of success, as discussed above and in my Initial Declaration. Also, I have considered potential secondary considerations relating to the 837 patent claims, but I do not believe that there are any secondary considerations that weigh against the obviousness of any claims.

60. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Respectfully submitted,



Richard B. Fair

Dated: November 11, 2020