10X Genomics Inc. (Petitioner) v. Bio-Rad Laboratories, Inc. (Patent Owner)

IPR2020-00086 (U.S. Patent No. 9,562,837) and
IPR2020-00088 (U.S. Patent No. 9,896,722)

Petitioner's Demonstratives
Ismagilov Grounds

10x GENOMICS®

January 27, 2021

Grounds

Grounds	References	Claims
1	Ismagilov 091 (§ 102)	837 Patent: 1-2, 4, 10-13, 19-20 722 Patent: 1-7, 10-11, 14
2	Ismagilov 091 and Quake (§ 103)	837 Patent: 1-2, 4, 7, 9-13, 19-20 722 Patent: 1-7, 10-17
3a, 3b	Ismagilov 119 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17
4a, 4b, 5a, 5b	Ismagilov 119 and Pamula 634/238 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17

Claim Constructions

- Grounds 1-2: Bio-Rad's Claim Constructions
- "a" Grounds: 10X's Claim Constructions
- "b" Grounds: Bio-Rad's Claim Constructions

IPR2020-00086 Petition at 23-25; IPR2020-00088 Petition at 22-24

837 Patent – Independent Claim 1

1. An assembly, the assembly comprising:

[1.1] a microchannel in a horizontal plane;

[1.2] at least one droplet formation module comprising a sample inlet, an immiscible fluid inlet, and a junction, wherein the junction is located between the sample inlet and the microchannel and the droplet formation module is configured to produce droplets comprising the sample surrounded by the immiscible fluid; and

[1.3] at least one downstream separation chamber comprising a droplet receiving chamber inlet and at least one droplet receiving outlet,
[1.4] wherein the separation chamber is upright to the microchannel and out of the horizontal plane;

[1.5] wherein the droplet formation module and the separation chamber are in fluid communication with each other via the microchannel; and
[1.6] wherein the separation chamber has a wider cross-section than the microchannel cross-section to accumulate a plurality of droplets comprising the sample and
[1.7] is of a volume sufficient to separate the plurality of droplets comprising the sample from the immiscible fluid within the separation chamber.

IPR2020-00086, Ex. 1001

722 Patent – Independent Claim 1

1. A method of reducing contamination associated with sample handling, comprising:

[1.1] providing an aqueous fluid comprising a sample through a sample inlet;

[1.2] providing an immiscible fluid flowing through a main channel that is in fluidic communication with the sample inlet, wherein the main channel is in a horizontal plane;

[1.3] partitioning the aqueous fluid with the immiscible fluid to form a plurality of droplets in the main channel, wherein at least one droplet comprises a sample;

[1.4] flowing the droplets toward a downstream separation chamber that is in fluidic communication with the main channel,

[1.5] wherein the separation chamber has a wider cross-section than the main channel cross-section and

[1.6] the separation chamber is disposed perpendicular to the main channel; and

[1.7] separating the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid.

IPR2020-00088, Ex. 1001

722 Patent – Independent Claim 14

14. A method of reducing sample loss associated with sample handling, comprising:

[14.1] providing an aqueous fluid comprising a sample through a sample inlet;

[14.2] providing an immiscible fluid flowing through a main channel that is in fluidic communication with the sample inlet, wherein the main channel is in a horizontal plane;

[14.3] partitioning the aqueous fluid with the immiscible fluid to form a plurality of droplets in the main channel;

[14.4] flowing the droplets toward a downstream separation chamber that is in fluidic communication with the main channel,

[14.5] wherein the separation chamber has a wider cross-section than the main channel cross-section and

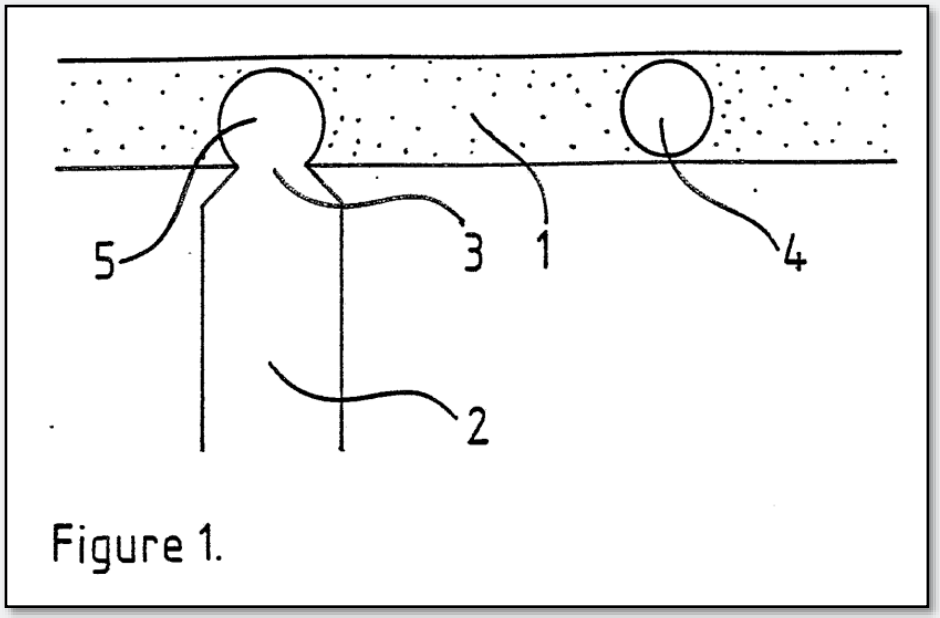
[14.6] the separation chamber is disposed perpendicular to the main channel; and

[14.7] separating the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid.

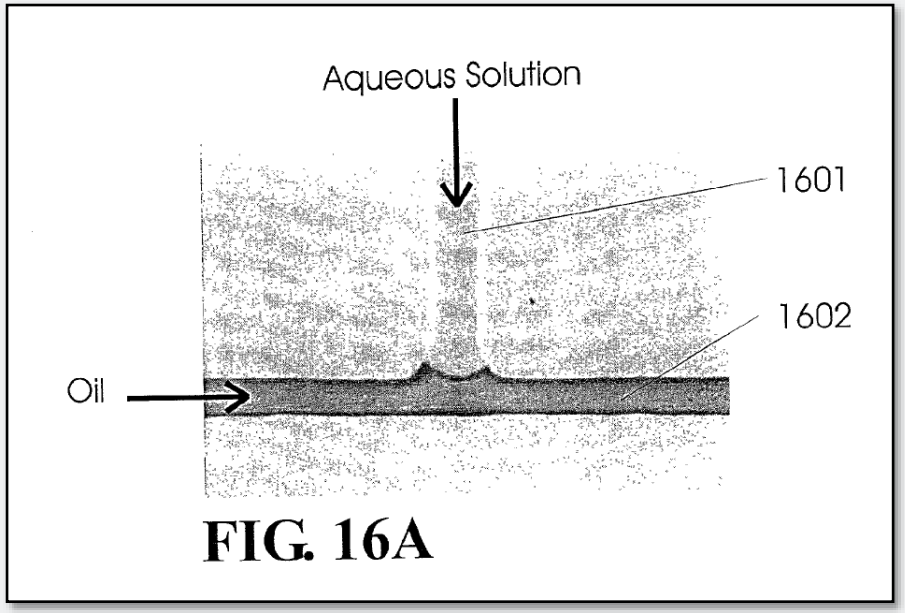
IPR2020-00088, Ex. 1001

Background: Microfluidic Droplet Generation Was Known

Stewart



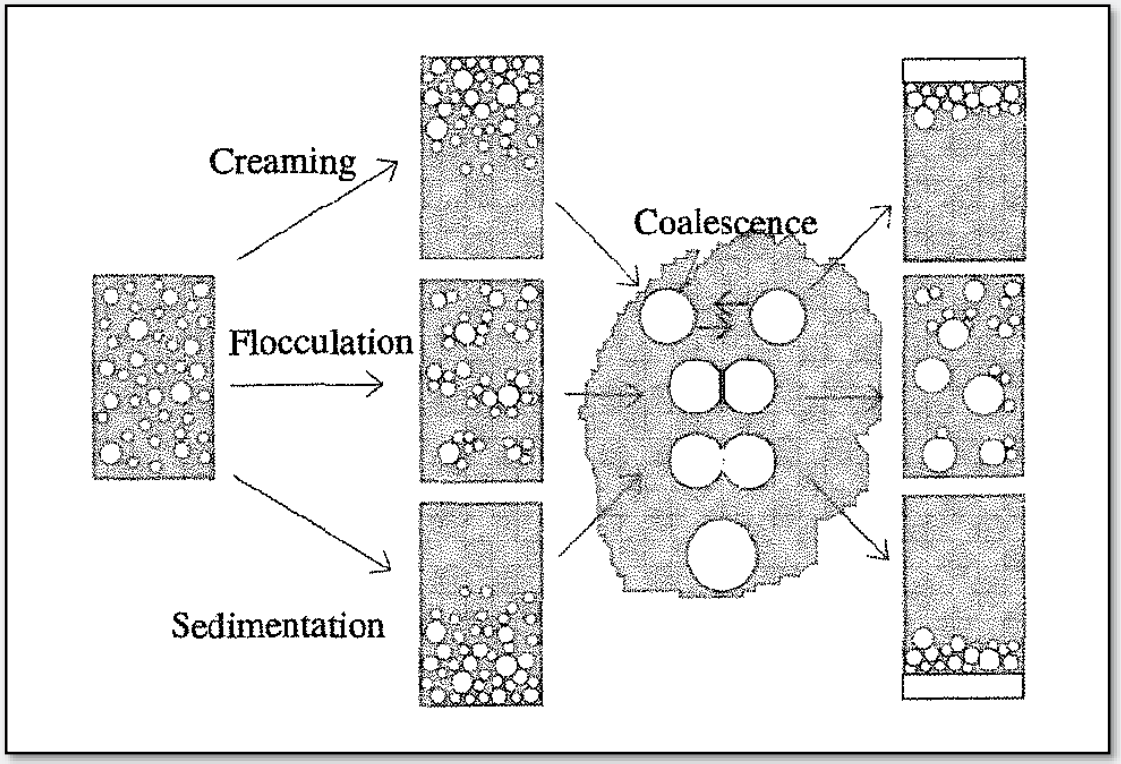
Quake



IPR2020-00086/88 Ex. 1048, Fig. 1; IPR2020-00086/88 Ex. 1006, Fig. 16A
IPR2020-00086 Petition at 6-7; IPR2020-00088 Petition at 5-6

Background: It Was Well-Known That Droplets Float Or Sink Based On Their Density

Encyclopedic Handbook of Emulsion Technology



IPR2020-00086 Ex. 1009 at 51; IPR2020-00088 Ex. 1009 at 51
IPR2020-00086 Petition at 8-9; IPR2020-00088 Petition at 8

Bio-Rad Claim Constructions

Term or Phrase	Bio-Rad Infringement Contention Construction	Bio-Rad's Proposed Construction
"separation chamber" (837 Patent, Claim 1; 722 Patent, Claims 1, 14)	Broad enough to encompass an open well	"chamber sized to accommodate multiple droplets and an immiscible fluid in separated form"
"droplet receiving outlet" (837 Patent, Claim 1)	Broad enough to include the opening at the top of an open outlet well	"portion of the separation chamber where droplets are collected"
"coupled" (837 Patent, Claims 7-8)	Broad enough to encompass transporting by pipette between an alleged outlet/chamber and vessel	"operably linked"

IPR2020-00086 Petition at 18-19; IPR2020-00088 Petition at 19
IPR2020-00086 PO Response at 18-28; IPR2020-00088 PO Response at 18-21

Grounds

Grounds	References	Claims
1	Ismagilov 091 (§ 102)	837 Patent: 1-2, 4, 10-13, 19-20 722 Patent: 1-7, 10-11, 14
2	Ismagilov 091 and Quake (§ 103)	837 Patent: 1-2, 4, 7, 9-13, 19-20 722 Patent: 1-7, 10-17
3a, 3b	Ismagilov 119 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17
4a, 4b, 5a, 5b	Ismagilov 119 and Pamula 634/238 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17

Claim Constructions

- Grounds 1-2: Bio-Rad's Claim Constructions
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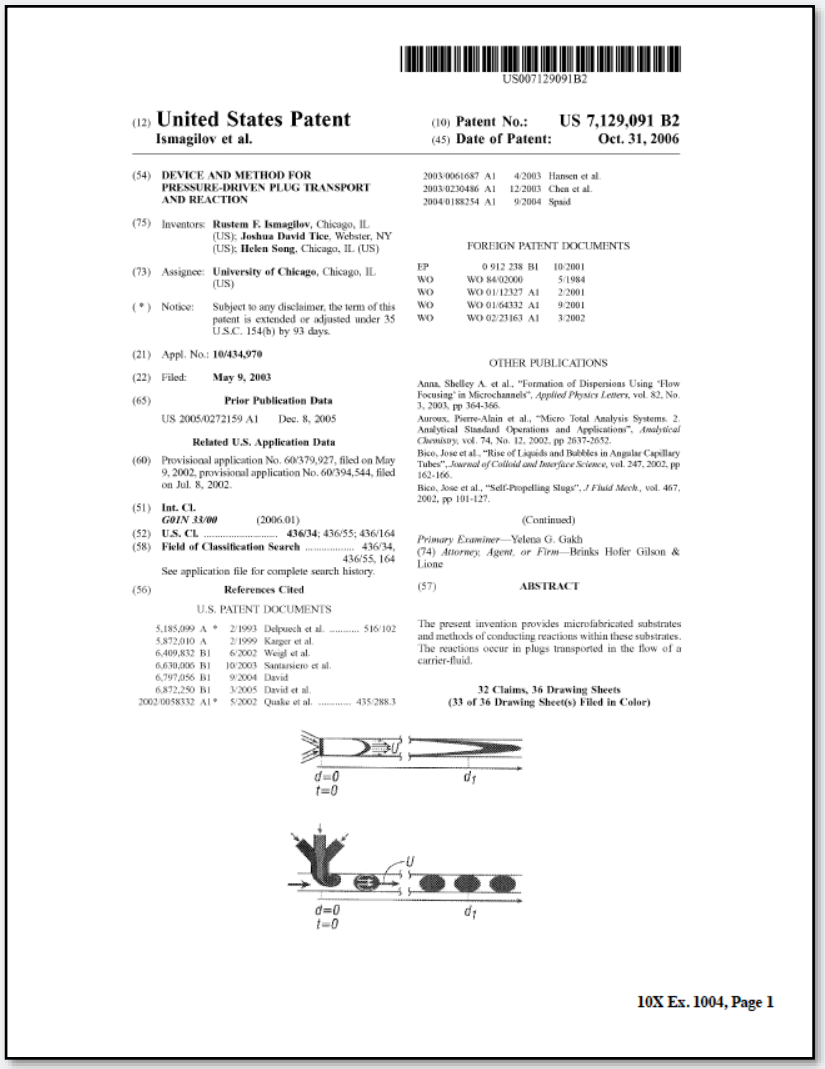
IPR2020-00086 Petition at 23-25; IPR2020-00088 Petition at 22-24

Ismagilov 091 Anticipates



US007129091B2

(12) **United States Patent**
Ismagilov et al.

(10) **Patent No.: US 7,129,091 B2**
(45) **Date of Patent: Oct. 31, 2006**

(54) **DEVICE AND METHOD FOR PRESSURE-DRIVEN PLUG TRANSPORT AND REACTION**

(75) Inventors: **Rustem F. Ismagilov**, Chicago, IL (US); **Joshua David Tice**, Webster, NY (US); **Helen Song**, Chicago, IL (US)

(73) Assignee: **University of Chicago**, Chicago, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 93 days.

(21) Appl. No.: **10/434,970**

(22) Filed: **May 9, 2003**

(65) **Prior Publication Data**

US 2005/0272159 A1 Dec. 8, 2005

Related U.S. Application Data

(60) Provisional application No. 60/379,927, filed on May 9, 2002, provisional application No. 60/394,544, filed on Jul. 8, 2002.

(51) **Int. Cl.**
G01N 33/00 (2006.01)

(52) **U.S. Cl.** **436/34**; 436/55; 436/164

(58) **Field of Classification Search** 436/34, 436/55, 164

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

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(Continued)

Primary Examiner—Yelena G. Gakh
(74) *Attorney, Agent, or Firm*—Brinks Hofer Gilson & Lione

(57) **ABSTRACT**

The present invention provides microfabricated substrates and methods of conducting reactions within these substrates. The reactions occur in plugs transported in the flow of a carrier-fluid.

32 Claims, 36 Drawing Sheets
(33 of 36 Drawing Sheet(s) Filed in Color)

10X Ex. 1004, Page 1

Ismagilov discloses all claim elements under Bio-Rad's reading of the claims:

- Ismagilov discloses the microfluidic generation of droplets containing reactants such as biological molecules
- Ismagilov discloses wells into which the droplets can flow and collecting droplets at outlets
- Ismagilov discloses droplets of different densities that inherently separate in the disclosed wells

IPR2020-00086 Petition at 7-12, 32-37; IPR2020-00088 Petition at 7-13, 30-37

Ismagilov 091 Discloses Microfluidic Droplet Generation

837 Claim 1

1. An assembly, the assembly comprising:

[1.1] a microchannel in a horizontal plane;

[1.2] at least one droplet formation module comprising a sample inlet, an immiscible fluid inlet, and a junction, wherein the junction is located between the sample inlet and the microchannel and the droplet formation module is configured to produce droplets comprising the sample surrounded by the immiscible fluid; and

722 Claim 1

1. A method of reducing contamination associated with sample handling, comprising:

[1.1] providing an aqueous fluid comprising a sample through a sample inlet;

[1.2] providing an immiscible fluid flowing through a main channel that is in fluidic communication with the sample inlet, wherein the main channel is in a horizontal plane;

[1.3] partitioning the aqueous fluid with the immiscible fluid to form a plurality of droplets in the main channel, wherein at least one droplet comprises a sample;

The different plug-forming regions may each be connected to the same or different channels of the substrate. Preferably, the sample inlet intersects a first channel such that the pressurized plug fluid is introduced into the first channel at an angle to a stream of carrier-fluid passing through the first channel. For example, in preferred embodiments, the sample inlet and first channel intercept at a T-shaped junction; i.e., such that the sample inlet is perpendicular (i.e. at an angle of 90°) to the first channel. However, the sample inlet may intercept the first channel at any angle.

Ismagilov 091 (IPR2020-00086/88 Ex. 1004), 14:54-61
IPR2020-00086 Petition at 32; IPR2020-00088 Petition at 30-31

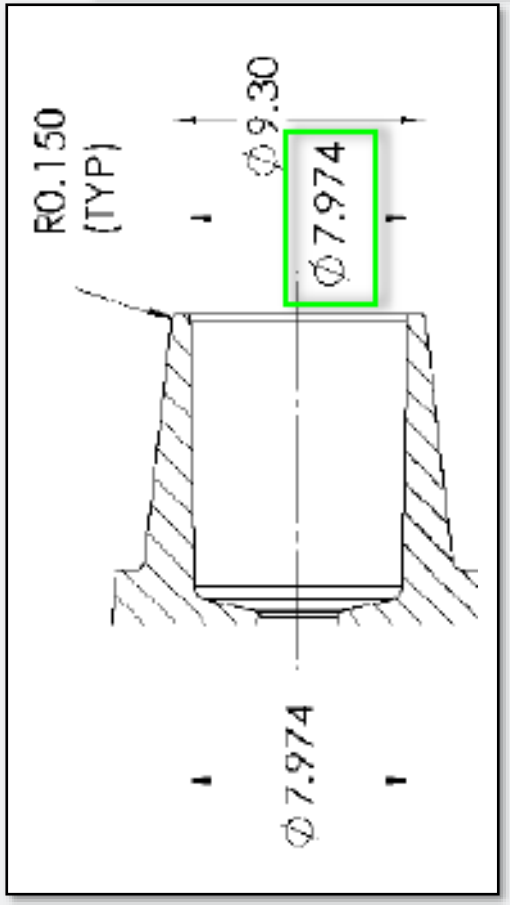
Ismagilov 091: Separation Chamber Disputes

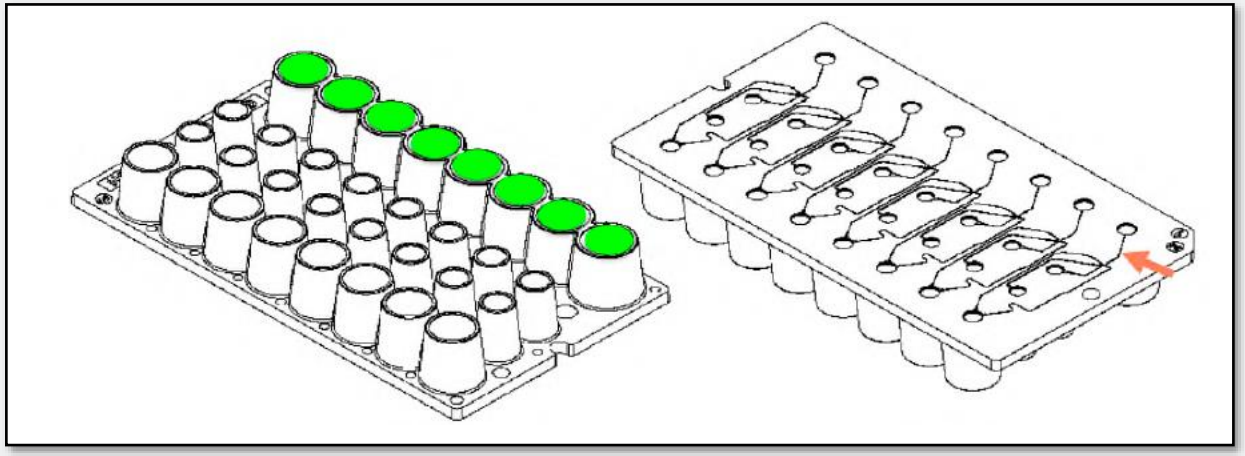
- Bio-Rad argues there is no "separation chamber" in Ismagilov (837 & 722 Patents)
- Bio-Rad argues that there is no disclosure of the structure of the separation chamber
- Bio-Rad argues that there is no volume sufficient to separate or separating

IPR2020-00086 PO Response at 29-43; IPR2020-00088 PO Response at 22-38

Bio-Rad's Infringement Contentions Accuse An Open Well Of Being A "Separation Chamber"

The 10X Double Junction Accused Products literally infringe this element because the separation chamber (green) is upright to the microchannel (orange arrow), and out of the horizontal plane:





IPR2020-00086 Petition at 18-19; IPR2020-00088 Petition at 19
IPR2020-00086 Ex. 1026, 12-13, 18

Ismagilov 091 Discloses A Separation Chamber

- The Board found sufficient disclosure of a separation chamber at institution
  - "As we understand it, Petitioner contends that a 'separation chamber' is disclosed by Ismagilov 091's well or reservoir. . . . In our view, Petitioner's contention is sufficiently supported by the cited disclosures of Ismagilov 091." (IPR2020-00086)
  - The Board cited to 10X's reliance on the following passages (9:5–8, 14:36–40, and 17:27–30)

IPR2020-00086 Institution Decision at 35; *see also* IPR2020-00088 Institution Decision at 34

Ismagilov 091 Discloses A Separation Chamber

- Ismagilov 091 discloses a separation chamber

> The term "outlet port" refers to an area of a substrate that collects or dispenses the plug-fluid, carrier-fluid, plugs or reaction product. A substrate may contain more than one

> The device may have one or more outlet ports or inlet ports. Each of the outlet and inlet ports may also communicate with a well or reservoir. The inlet and outlet ports may be in fluid communication with the channels or reservoirs that they are connecting or may contain one or more valves.

Ismagilov 091 (IPR2020-00086 & IPR2020-00088 Ex. 1004), 9:5-7, 14:36-40
IPR2020-00086 Petition at 35-37, 40-41, 44, 46; IPR2020-00088 Petition at 35-37, 41-43

Ismagilov 091 Discloses A Separation Chamber

Dr. Richard Fair

Duke UNIVERSITY

- 10X's Expert Dr. Fair explains that Ismagilov 091 discloses a separation chamber

> 11. Under Bio-Rad's interpretation, Ismagilov 091 discloses collection wells or reservoirs that are a separation chamber with a droplet receiving outlet. Ismagilov 091 discloses an "outlet port" which is "an area of a substrate that ***collects*** or dispenses . . . plugs" and may "communicate with a ***well or reservoir***." Ismagilov 091, 9:5-8, 14:36-38. Ismagilov similarly describes after a manifold an outlet, and

IPR2020-00086 Ex. 1008, ¶ 129; *see also* IPR2020-00088 Ex. 1008, ¶ 127
IPR2020-00086 Petition at 35-36; IPR2020-00088 Petition at 35-37

Ismagilov 091: Separation Chamber Disputes

- Bio-Rad argues there is no separation chamber
- Bio-Rad argues that there is no disclosure of the specific structure of the separation chamber
  - "***upright*** to the microchannel and out of the horizontal plane" (837 Patent) / "disposed ***perpendicular*** to the main channel" (722 patent)
  - "a ***wider cross-section*** than the microchannel cross-section to accumulate a plurality of droplets" (837 Patent) / "***wider cross-section*** than the main channel cross-section" (722 Patent)
  - "a droplet receiving chamber inlet and at least one **droplet receiving outlet**" (837 Patent)
- Bio-Rad argues that there is no volume sufficient to separate or separating

IPR2020-00086 PO Response at 29-43; IPR2020-00088 PO Response at 22-38

Ismagilov 091 Discloses The Structure of A Separation Chamber

- The Board found the separation chamber structure was disclosed at institution
  - "Although Patent Owner argues that Ismagilov 091 does not disclose 'any chamber with the dimensions and configuration claimed in the '837 patent,' Patent Owner does not adequately address Petitioner's contention that Ismagilov 091 discloses a well or reservoir with an opening at the top into which a micropipette can be inserted, and that this structure discloses a "separation chamber" and "droplet receiving outlet" under Patent Owner's interpretation of these terms in its infringement contentions." (837 Patent)

IPR2020-00086 Institution Decision at 35

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- The Board found the separation chamber structure was disclosed at institution

record, we disagree. Regarding the dimensions and configuration of Ismagilov 091's well or reservoir, Petitioner contends, *inter alia*:

> The extension of the well or reservoir out of the horizontal plane of the microchannels is confirmed because the volume of an outlet well or reservoir in Ismagilov [091] must permit collecting multiple droplets and must be large enough that the fluid can be collected by micropipette. . . . A volume sufficient to collect by micropipette must be greater than 0.1 µl. . . . By contrast, examples of droplets in Ismagilov [091] are as small as 16 pL, and so this well or reservoir would collect multiple droplets and extend above the channels, which are shown as not having a cross-section that can accommodate multiple droplets. . . . To be pipetted, the volume to be collected would need to be deep enough for the pipette to extend into it, and so the wells or reservoirs must extend vertically, perpendicular to the horizontal plane of the microchannels.

Pet. 43 (citing Ex. 1004, 17:27–30, 19:61–66, Figs. 2–10; Ex. 1008 ¶ 152, 155–156; Ex. 1040, Ex. 1041, 1); *see also id.* (stating because Ismagilov 091 describes closing the channels with a glass coverslip, the well or reservoir would extend perpendicular to the plan of the microchannels (citing Ex. 1004, 16:37–41, 30:2–9). At this stage, we view Petitioner's evidence and technical reasoning as sufficient to support its contentions regarding the dimensions and configuration of the well or reservoir disclosed by Ismagilov 091.

IPR2020-00088 Institution Decision at 35; *see also* IPR2020-00086 Institution Decision at 36

Ismagilov 091 Chip Fabrication Method Confirms the Wells Are "upright" / "perpendicular"

- Because the channels are closed by a bottom glass coverslip, the substrate structures extend vertically ("upright" or "perpendicular")

> of HCl if it is desired to render the surface hydrophilic. The PDMS channels can then be placed onto a microscope cover slip (or any other suitable flat surface), which can be used to form the base/floor or top of the channels.

Ismagilov 091 (IPR2020-00086 & IPR2020-00088 Ex. 1004), 16:38-41
IPR2020-00086 Petition at 31, 40-41; IPR2020-00088 Petition at 34, 43,

Ismagilov 091 Chip Fabrication Method Confirms the Wells Are "upright" / "perpendicular"

Dr. Richard Fair

Duke UNIVERSITY

- 10X's expert Dr. Fair explains that because the channels are closed by a bottom glass coverslip, the substrate structures extend vertically ("upright" or "perpendicular")

8:41-44, 9:5-8, 14:36-38, 27:53-58, 28:67-29:5. As I explained for limitation 1.3, Ismagilov 091 describes forming the substrate, closing the channels with a glass coverslip, and placing the glass coverslip down. Based on both of these disclosures, the well or reservoir would extend up and out of the plane of the microchannels. *See* Ismagilov 091, 16:37-41, 30:2-9. When the glass coverslip is placed flat down, the channels are adjacent to the coverslip. Generally, structures will not extend down through the glass coverslip. Thus, if there is a well, it will be extending upward and out of the plane of the microchannels to permit the collection of multiple droplets and to collect a volume sufficient to be pipetted.

IPR2020-00086 Ex. 1008, ¶ 160; *see also* IPR2020-00088 Ex. 1008, ¶¶ 155-57
IPR2020-00086 Petition at 31, 40-41; IPR2020-00088 Petition at 34, 43,

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- Ismagilov 091 discloses a "well"

> The device may have one or more outlet ports or inlet ports. Each of the outlet and inlet ports may also communicate with a well or reservoir. The inlet and outlet ports may be in fluid communication with the channels or reservoirs that they are connecting or may contain one or more valves.

Ismagilov 091 (IPR2020-00086 & IPR2020-00088 Ex. 1004), 9:5-7, 14:36-40
IPR2020-00086 Petition at 41; IPR2020-00088 Petition at 43-44

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

Dr. Richard Fair

Duke UNIVERSITY

- Dr. Fair explained that a "well" has the structure of a separation chamber

> Second, a well for collecting droplets would similarly need to extend vertically out of the plane of the microchannels. Ismagilov 091, 8:41-44, 9:5-8, 14:36-38. Thus, the outlet well will necessarily be extending upward and out of the plane of the microchannel because it will not extend down through the glass cover slip and it will need to extend upward to the top of the substrate in order to be an open well (as opposed to a closed cavity or chamber). A person of ordinary skill in the art would understand the disclosure of an outlet "well" to refer to an open-topped, bucket-like structure from which the accumulated droplets could be extracted, e.g., by using a micropipette. Thus, a well to "collect[]" droplets would extend vertically out of the plane of the microchannels to serve the purpose of holding multiple droplets in a vertical volume such that they can then be used downstream.

IPR2020-00086 Ex. 1008 (Fair Decl.), ¶ 161
IPR2020-00086 Petition at 40-41; IPR2020-00088 Petition at 43-44

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

Dr. Richard Fair

Duke UNIVERSITY

- Dr. Fair explained that a "well" has the structure of a separation chamber

> of the microchannels to permit that. Second, a well for collecting droplets would similarly need to extend vertically out of the plane of the microchannels. Ismagilov, 8:41-44, 9:5-8, 14:36-38. If this was not the case and the "well" was wide but shallow and only rose to the height of the microchannels, such a structure would not "collect[]" droplets in any meaningful or practical sense of that word. It would be spilling them onto a surface. Thus, a well to "collect[]" droplets would extend vertically out of the plane of the microchannels to serve the purpose of holding multiple droplets in a vertical volume such that they can then be used downstream.

IPR2020-00088 Ex. 1008 (Fair Decl.), ¶ 156
IPR2020-00086 Petition at 40-41; IPR2020-00088 Petition at 43-44

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- Ismagilov discloses collection by micropipette

> the flow of solution to an outlet. The outlet can be adapted for receiving, for example, a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube. Collection can also be done using micropipettes.

Ismagilov 091 (IPR2020-00086 & IPR2020-00088 Ex. 1004), 17:27-30
IPR2020-00086 Petition at 35-37, 40-41, 44-46; IPR2020-00088 Petition at 35-37, 41-42, 43-44

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- Ismagilov discloses collection by micropipette

> the flow of solution to an outlet. The outlet can be adapted for receiving, for example, a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube. Collection can also be done using micropipettes.

- Bio-Rad accused the opening of the well of the 10X product into which a micropipette is inserted as the claimed 837 Patent "droplet receiving outlet"

> The separation chamber also comprises a droplet receiving outlet for removing the droplets from the separation chamber following droplet generation, which is shown below as the location where the pipette is inserted to remove the "GEMs":

IPR2020-00086 Ex. 1026, 11; Ismagilov 091 (IPR2020-00086 Ex. 1004), 17:27-30
IPR2020-00086 Petition at 35-36

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

Dr. Richard Fair

Duke UNIVERSITY

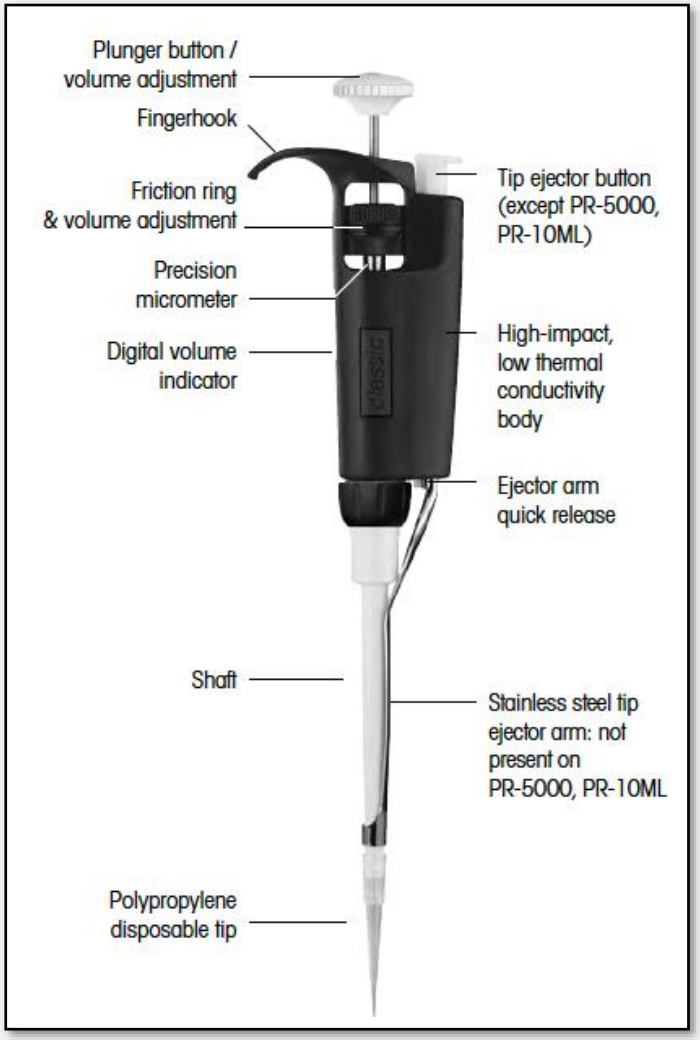
10X's Expert Dr. Fair explained the volume sufficient to use a micropipette, confirming the separation chamber structure that is wide and "upright" / "perpendicular"

161. The extension of the well or reservoir out of the horizontal plane of the microchannels is further confirmed by the fact that the volume of an outlet well or reservoir in Ismagilov 091 must permit collecting multiple droplets and must be large enough that the fluid can be collected by micropipette. Ismagilov 091, 17:27-30. First, a micropipette can collect down to 0.1 µl. Ex. 1040, Ex. 1041. This is the minimum possible volume to pipette, but in practice larger volumes are typically used. If there is only a small volume or a volume spread across a surface, a micropipette will not be able to collect the liquid because air will enter the micropipette tip instead of liquid. To pipette liquid, the tip of the micropipette must be completely inserted into the liquid volume. There must therefore be a sufficiently deep and wide well for the pipette to enter and then collect the liquid. Thus, the well will need to be larger than the 0.1 µl minimum volume that a micropipette can collect. By contrast, examples of droplets in Ismagilov 091 are as small as 16 pL, and so this well or reservoir would collect multiple droplets and extend above the channels, which are shown as not having a cross-section that can accommodate multiple droplets. *E.g.*, Ismagilov 091, 19:61-66, Figs. 2, 10. In order to be pipetted, the volume to be collected would need to be deep enough for the pipette to extend into it, and so the wells or reservoirs will extend out of the horizontal plane to permit that.

IPR2020-00086 Ex. 1008, ¶ 161; *see also* IPR2020-00088 Ex. 1008, ¶ 156
IPR2020-00086 Petition at 41; IPR2020-00088 Petition at 43-44

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- Dr. Fair relied on an exhibit that showed a micropipette (Ex. 1040)



IPR2020-00086 Ex. 1040 at 3; IPR2020-00088 Ex. 1040 at 3
IPR2020-00086 Petitioner Reply at 15-16; IPR2020-00088 Petitioner Reply at 14

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- There is no dispute that the image shows a micropipette
- Bio-Rad's expert admitted that this image is of a micropipette

> explains they would be created. Although Dr. Fair shows an image of a micropipette in his declaration, he never discloses the size of the "polypropylene disposable tip" or discusses whether it would fit into the outlet openings of the Ismagilov that Petitioner asserts to be the "separation chamber." Nor do the

- Bio-Rad admits the same in its Patent Owner Response

IPR2020-00086 Ex. 2016 (Anna Decl.), ¶ 131; IPR2020-00088 Ex. 2016, ¶ 113
IPR2020-00086 PO Response at 37; IPR2020-00088 PO Response at 29-30
IPR2020-00086 Petitioner Reply at 15-16; IPR2020-00088 Petitioner Reply at 14

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- Bio-Rad argues that there is no disclosure of the structure of the separation chamber
  - Bio-Rad argues micropipette collection could be performed horizontally
  - Bio-Rad argues that other references show micropipettes that could be placed in smaller holes
- Bio-Rad is incorrect
  - Micropipettes cannot be operated horizontally and require a vertical well as described
  - The references Bio-Rad relies upon do not describe a "micropipette"
  - Bio-Rad has stated that a micropipette cannot be placed in a smaller hole, contradicting its expert

IPR2020-00086 PO Response at 34-36; IPR2020-00088 PO Response at 27-29
IPR2020-00086 Petitioner Reply at 4-20; IPR2020-00088 Petitioner Reply at 2-19

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

- Micropipettes cannot be operated horizontally

5. Holding Rainin Classic vertically, immerse the tip into the sample to the proper depth; see table on page 4.

5. Minimal angle (< 20° from vertical).

Prevent liquids from being drawn into the shaft by taking the following precautions:

1. Use Rainin aerosol-resistant tips, with an internal filter which acts as a barrier to aerosols and liquids.
2. Never invert or lay the pipette down if liquid is in the tip.
3. Pipette slowly, holding the pipette < 20° from vertical.

IPR2020-00086/88 Ex. 1040 at 5-7
IPR2020-00086 Petitioner Reply at 15-16; IPR2020-00088 Petitioner Reply at 14

Ismagilov 091 Wells Created By Cork Borers

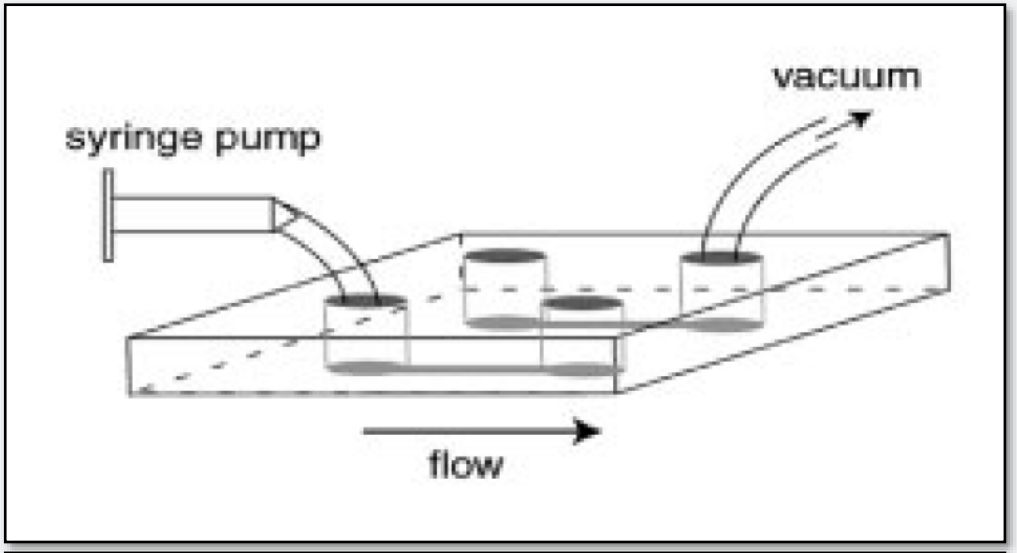
- Bio-Rad's expert admits that Ismagilov's outlet ports and wells or reservoirs were commonly known and created with cork borers

> 35. In my opinion, the references to "outlet ports" or "wells or reservoirs" that are relied upon by Petitioner in the 086 Petition are not disclosing any new design or configuration, but are merely referencing commonly known elements of microfluidic devices from the time of the disclosed invention in the early 2000's that I describe below. This is evidenced by the reference to the use of cork borers or syringe needles to cut holes into the PDMS when preparing the devices. (Ex. 1004 at 16:35-36).

IPR2020-00086 Ex. 2016, ¶ 35; IPR2020-00088 Ex. 2016, ¶ 35
IPR2020-00086 PO Response at 9; IPR2020-00088 PO Response at 8-9
IPR2020-00086 Petitioner Reply at 7-8; IPR2020-00088 Petitioner Reply at 6

Cork Borer Wells

- Wells made by cork borers in Ismagilov further confirm that Ismagilov 091 disclosed a vertically extended separation chamber wider than the channels
- Bio-Rad relied on an exhibit that showed and described the wells made by cork borers



Small holes are drilled into the PDMS using a borer to produce inlets and outlets. Finally, PDMS can seal to itself

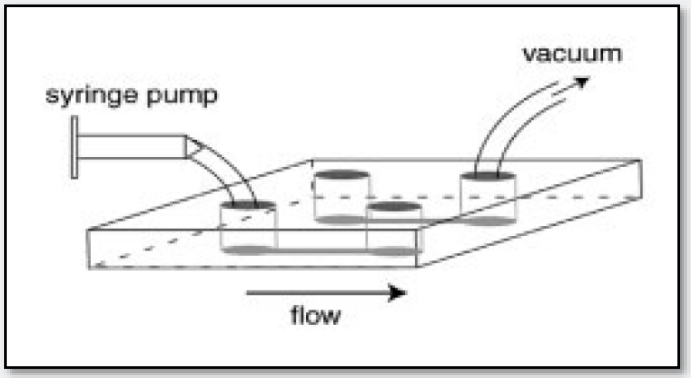
IPR2020-00086/88 Ex. 2033 at 2-3
IPR2020-00086 Petitioner Reply at 8; IPR2020-00088 Petitioner Reply at 7

Cork Borer Wells

- Bio-Rad's expert admitted that it showed the holes that a cork borer could make

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.

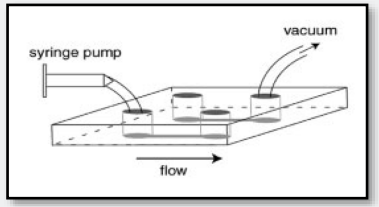


IPR2020-00086/88 Ex. 1075 (Anna Depo) at 114:23-115:3
IPR2020-00086 Petitioner Reply at 8; IPR2020-00088 Petitioner Reply at 6-7

Cork Borer Wells

- Bio-Rad's expert explained that the figure showed gray channels and the cork borer holes through the substrate

> [Q.] Would your interpretation of that be that those gray lines are channels connecting those different holes?
>
> A. Well, you know, I'd have to look closely at what the reference defines it as, but generally speaking I would interpret -- that's how I would interpret that.
>
> 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.



IPR2020-00086/88 Ex. 1075 (Anna Depo) at 114:3-114:22
IPR2020-00086 Petitioner Reply at 8; IPR2020-00088 Petitioner Reply at 7

Ismagilov 091 Wells Made By Cork Borers

- Ismagilov disclosed thick substrates through which a cork borer well would extend to result in an "upright" / "perpendicular" separation chamber

microchip, or silicone elastomers. The dimensions of the substrate may range, for example, between about 0.3 cm to about 7 cm per side and about 1 micron to about 1 cm in thickness, but other dimensions may be used.

IPR2020-00086/88 Ex. 1004 (Ismagilov 091), 16:44-47
IPR2020-00086 Petitioner Reply at 10-11; IPR2020-00088 Petitioner Reply at 8-10

Ismagilov 091 Wells Made By Cork Borers

- Bio-Rad argues that there is no disclosure of the structure of the separation chamber
  - Bio-Rad's expert argued that a 1 mm micropipette tip would be "larger than the size of a punch hole created by the standard techniques from that timeframe disclosed in Ismagilov using a syringe needle or cork borer."

- Bio-Rad is incorrect
  - Bio-Rad's expert did not know the available sizes of cork borers
  - Dr. Fair explained that cork borers larger than 1 mm were available, and so cork borer wells in Ismagilov were not limited to 1 mm

IPR2020-00086 Ex. 2016, ¶ 132; IPR2020-00088 Ex. 2016, ¶ 114
IPR2020-00086 Petitioner Reply at 8; IPR2020-00088 Petitioner Reply at 7

Ismagilov 091 Wells Made By Cork Borers

- Bio-Rad's expert did not know the available sizes of cork borers

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.

IPR2020-00086/88 Ex. 1075 (Anna Dep.) at 84:24-85:6
IPR2020-00086 Petitioner Reply at 9; IPR2020-00088 Petitioner Reply at 8

Ismagilov 091 Wells Made By Cork Borers

Dr. Richard Fair

Duke UNIVERSITY

- Dr. Fair explained that cork borers larger than 1 mm were available, and so cork borer wells in Ismagilov were not limited 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

- Dr. Fair cited as support:
  - Ex. 1006 (Quake): "the wells are 2 mm in diameter
  - Ex. 1076 (Sia, Whitesides): "drill a hole (~4 mm in diameter)"
  - Exs. 1077-79: examples of cork borers

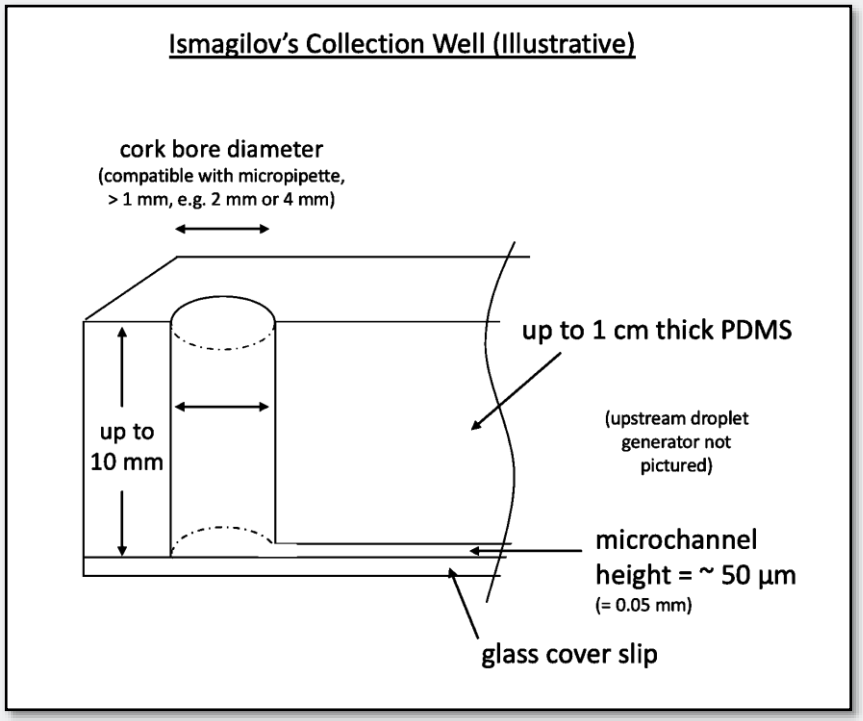
IPR2020-00086 Ex. 1071, ¶¶ 31-32; *see also* IPR2020-00088 Ex. 1073, ¶¶ 27-28
IPR2020-00086 Petitioner Reply at 9-10; IPR2020-00088 Petitioner Reply at 8-9

Ismagilov 091 Discloses An "upright" / "perpendicular" And Wide Separation Chamber

Dr. Richard Fair

Duke UNIVERSITY

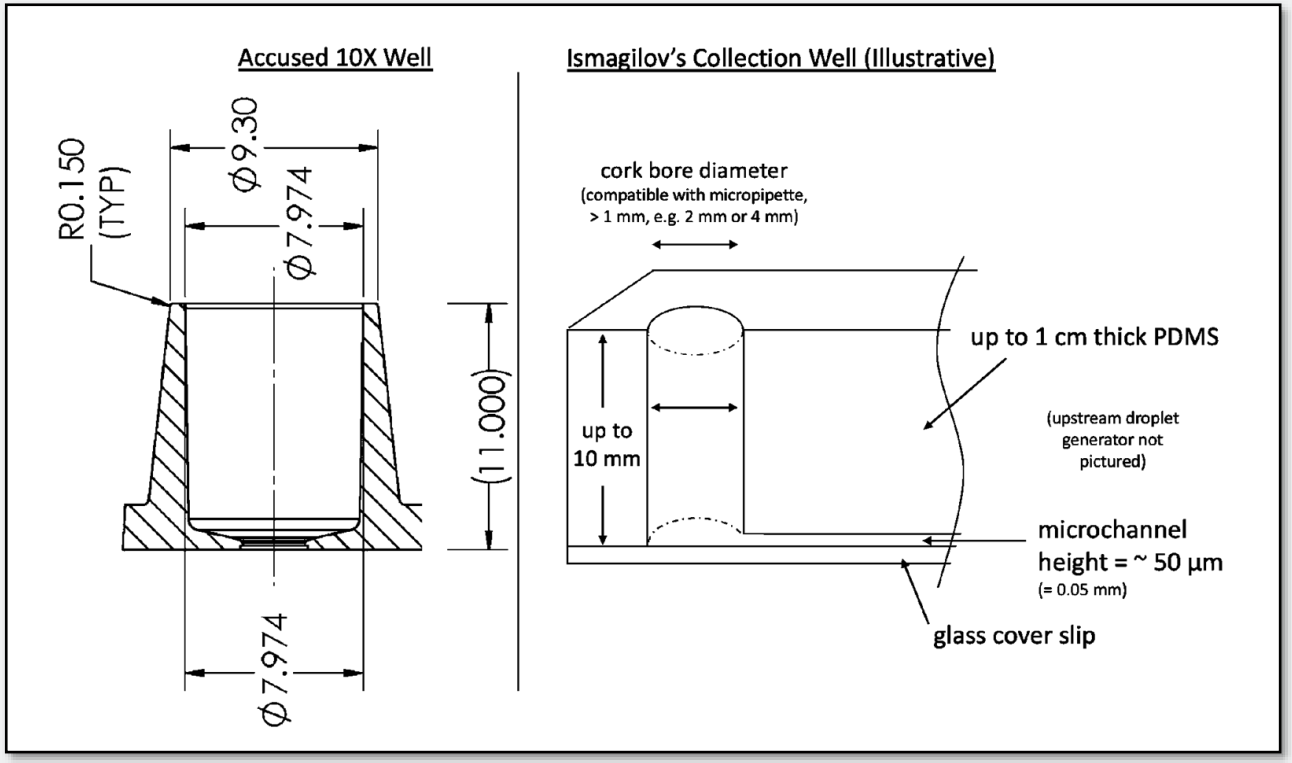
- Dr. Fair's illustrative of the Ismagilov cork borer wells shows the relevant dimensions, confirming the well is "upright" / "perpendicular" and wider than the channels



IPR2020-00086 Ex. 1071 (Fair Responsive Decl.) ¶ 37; IPR2020-00088 Ex. 1073 ¶ 33
IPR2020-00086 Petitioner Reply at 11; IPR2020-00088 Petitioner Reply at 10

Ismagilov 091 Wells Are Similar To The Accused Wells

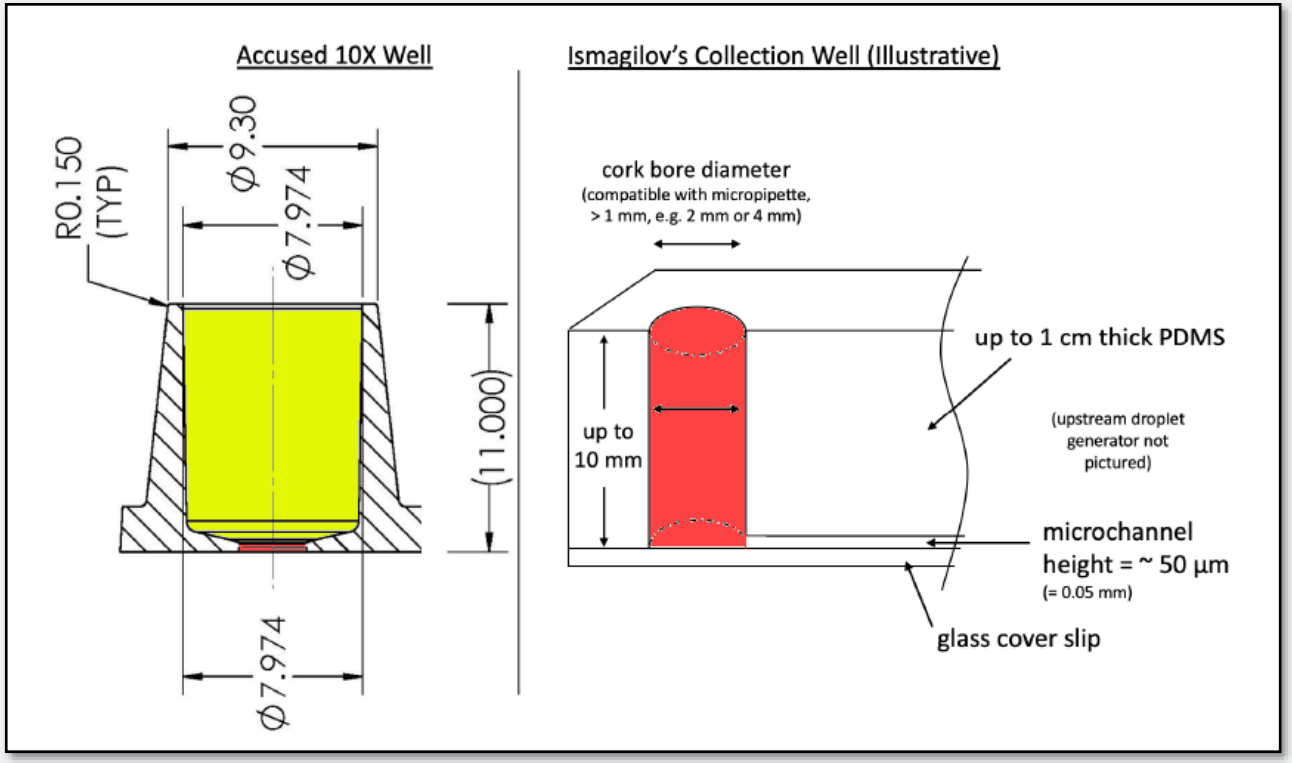
- The 10X and Ismagilov wells have similar dimensions, further reinforcing there is no relevant difference between the accused product and prior art



IPR2020-00086 Petitioner Reply at 13; IPR2020-00088 Petitioner Reply at 12

Ismagilov 091 Wells Are Similar To The Accused Wells

- There is no distinction relevant to the claims between the what **Bio-Rad** colored yellow and red in these similar wells



IPR2020-00086 PO Sur-Reply at 13; IPR2020-00088 PO Sur-Reply at 13

Ismagilov 091 Discloses The Structure of A Separation Chamber

- Bio-Rad argues that there is no disclosure of the structure of the separation chamber
  - Ismagilov's disclosures on "outlet ports" and "outlets" cannot be read together

- Bio-Rad is incorrect
  - The individual passages can be read together as part of the same disclosure
  - The passages are in sections about the same Ismagilov 091 disclosure: sections defining terms (7:23-11:18), describing "Channels and Devices" (14:20-15:67) and describing "Fabrication of Channels, Substrates, and Devices" (16:1-17:30)

IPR2020-00086 PO Response at 29-44; IPR2020-00088 PO Response at 22-38
Ismagilov 091 (IPR2020-00086/88 Ex. 1004)
IPR2020-00086 Petitioner Reply at 5-6; IPR2020-00088 Petitioner Reply at 4

10X's Arguments In Reply Should Not Be Excluded Or Ignored

- Bio-Rad argued in sur-reply that "new" arguments in reply should not be considered

- Bio-Rad is incorrect
  - Rebuttal of the institution decision and PO's Response is permitted, as is rebuttal evidence submitted in support of a reply. *See* 2019 Trial Practice Guide, 73.
  - 10X rebutted Bio-Rad's arguments on cork borers and showed how Bio-Rad's admissions confirm that Ismagilov discloses a separation chamber
  - Bio-Rad's second deposition of Dr. Fair and sur-reply were more than an adequate opportunity to respond
  - Bio-Rad did not move to exclude

IPR2020-00086 PO Sur-Reply at 3, 8-9; IPR2020-00088 PO Sur-Reply at 3, 8-9

Ismagilov 091: Separation Chamber Disputes

- Bio-Rad argues there is no separation chamber
- Bio-Rad argues that there is no disclosure of the structure of the separation chamber
- Bio-Rad argues that there is no volume sufficient to separate or separating
  - "***volume sufficient to separate*** the plurality of droplets comprising the sample from the immiscible fluid within the separation chamber" (837 Patent) / "***separating*** the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid" (722 Patent)

IPR2020-00086 PO Response at 29-44; IPR2020-00088 PO Response at 22-38

Ismagilov 091: Separation

- The Board at institution found the Ismagilov 091 ground supported by the evidence, noting that 10X relied on the separation of fluids of different densities
  - "Petitioner contends that claim element 1.7 is met because Ismagilov 091's outlet well or reservoir 'collects both a plurality of droplets and a volume of immiscible fluid" and "[t]hose droplets have a density different from that of the immiscible fluid,' meaning that the droplets will separate from the immiscible fluid in the outlet well or reservoir." (IPR2020-00086)
    - "Petitioner's mapping of claim 1 to the disclosures of Ismagilov 091 is sufficiently supported by the evidence."
  - "Petitioner asserts Ismagilov 091's output well or reservoir collects both droplets and immiscible fluid and that the aqueous droplets will float in the immiscible fluid (fluorinated oil). Pet. 45–46 (citing Ex. 1004, Figs. 2–10; Ex. 1026, 20–22; Ex. 1008 ¶¶ 162–163); *see also id*. at 45–46 (stating it is inherent that the droplets will either float or sink relative to the oil because the liquids have different densities)." (IPR2020-00088)
    - "In our view, Petitioner's contention is sufficiently supported by the cited disclosures of Ismagilov 091."

IPR2020-00086 Institution Decision at 34-35; IPR2020-00088 Institution Decision at 34

Ismagilov 091: Separation

relative to polar and non-polar solvents. In a preferred embodiment, the solvent may be an aqueous buffer solution, such as ultrapure water (e.g., 18 MΩ resistivity, obtained, for example, by column chromatography), 10 mM Tris HCl, and 1 mM EDTA (TE) buffer, phosphate buffer saline or acetate buffer. Other solvents that are compatible with the reagents

Suitable carrier-fluids include oils, preferably fluorinated oils. Examples include viscous fluids, such as perfluoro-decaline or perfluoroperhydrophenanthrene; nonviscous fluids such as perfluorohexane; and mixtures thereof (which are particularly useful for matching viscosities of the carrier-fluids and plug-fluids). Commercially available fluorinated

Ismagilov 091 (IPR2020-00086/88 Ex. 1004), 20:17-22, 20:37-42
IPR2020-00086 Petition at 10, 45-46; IPR2020-00088 Petition at 9, 45-46

Ismagilov 091: Separation

Dr. Richard Fair

Duke UNIVERSITY

- Dr. Fair explained that droplets inherently separate based on density, which confirms that all limitations of the independent claims are met under Bio-Rad's reading

71:53-62, 74:6-15. Aqueous (water) solutions and fluorinated oils have different densities. Ex. 1013 at 2 ("Coalescence of water droplets in a fluorocarbon phase should be favored by the ***large difference in densities*** . . . ."). Water has a density of 1 g/ cm^3, while perfluorohexane and perfluorodecaline have densities of around 1.7 and 1.9 g/cm^3, respectively. Ex. 1014, 4-5. These are constant, unchanging properties of these chemicals, and this difference in density means that such fluids would necessarily separate by less dense water droplets floating in denser oil. By

IPR2020-00086 Ex. 1008, ¶ 57; IPR2020-00088 Ex. 1008, ¶ 59
IPR2020-00086 Petition at 9, 45-46; IPR2020-00088 Petition at 9-10, 45-46

Ismagilov 091: Separation

- Bio-Rad argues that there is no volume sufficient to separate or separating
  - Bio-Rad argues there will be no separating if the selected oil has substantially the same density as water and thus separation is not inherent

- Bio-Rad is incorrect
  - Ismagilov expressly discloses water droplets in fluorinated oil, the inherent property of the fluids is that the lighter fluid will float
  - Bio-Rad identifies no droplets and oil disclosed in Ismagilov that do not separate

IPR2020-00086 PO Response at 42-43; IPR2020-00088 PO Response at 34-35
IPR2020-00086 Petitioner Reply at 18-20; IPR2020-00088 Petitioner Reply at 16-19

Ismagilov 091: Separation

- Bio-Rad argues that there is no volume sufficient to separate or separating
  - Bio-Rad argues there is no separation

- Bio-Rad is incorrect
  - For the 837 Patent, separation is not required under Bio-Rad's constructions because Bio-Rad argued against a district court construction saying it does "not require separation to occur"
  - Ismagilov discloses that collection of droplets/plugs can "be done using micropipettes"—precisely what Bio-Rad alleges satisfies the "separating" or "volume sufficient to separate" limitation for infringement.
  - Bio-Rad's expert confirmed that Bio-Rad's construction of droplet receiving outlet places no restriction on "how much droplet and how much other material" is received at the droplet receiving outlet (IPR2020-00086/88 Ex. 1075, 156:4-14, 153:16-160:8)

IPR2020-00086 Petitioner Reply at 14; IPR2020-00088 Petitioner Reply at 16; IPR2020-00086 Ex. 1026, 11-12, 16-20
IPR2020-00086 Ex. 1082, PO's Claim Construction Reply, 27; IPR2020-00088 Ex. 1026, 19-22

Ismagilov 091: Ground 1 Dependent Claims Without Additional Disputes

- Bio-Rad raised no argument regarding the following dependent claims other than those made for the independent claims, and so the following dependent claims rise or fall with the independent claims
  - 837 Patent Claims: 2, 4, 10-13, 19-20
  - 722 Patent Claims: 10-11

IPR2020-00088 PO Response at 43-44; IPR2020-00088 PO Response at 35-37

Ismagilov 091: Dependent Claims Disputes

- Bio-Rad disputes that 722 Patent Claims to "collecting the separated droplets" (722 Patent claim 2) / "wherein the separated droplets are collected into a vessel" (722 Patent claim 3) are anticipated by Ismagilov
  - Bio-Rad argues that Ismagilov does not refer to collecting separated droplets in a vessel such as a tube

IPR2020-00088 PO Response at 35-37
IPR2020-00088 Petitioner Reply at 19

Ismagilov 091: Claims 2/3 Are Disclosed

- Ismagilov 091 discloses several applications that require collecting separated droplets in a vessel

high-throughput screening. Highly parallel arrays of microfluidic systems are used for the synthesis of macroscopic quantities of chemical and biological compounds, e.g., the destruction of chemical warfare agents and pharmaceuticals synthesis. Their advantage is improved control over mass

Using the above devices and techniques, a variety of reactions can be conducted, including polymerizations, crystallizations (including small molecule and proteins), nanoparticle synthesis, formation of unstable intermediates, enzyme-catalyzed reactions and assays, protein—protein binding, etc. More than one reaction can be conducted,

The devices and methods according to the present invention may also be used for synthesizing polymers. Since the

Ismagilov 091 (IPR2020-00088 Ex. 1004), 1:24-28, 3:36-41, 50:51-52
IPR2020-00088 Petition at 46-47; PO Response at 35-37; IPR2020-00088 Petitioner Reply at 19

Ismagilov 091: Claims 2/3 Are Disclosed

Dr. Richard Fair

Duke UNIVERSITY

- Dr. Fair explained that the purpose of collecting droplets by micropipette is to transfer them

1:24-28, 3:36-41, 50:51-52. Indeed, the purpose of collecting droplets by micropipette will be to then transfer the droplets and collect them in a suitable vessel suitable for such collection.

IPR2020-00088 Ex. 1008, ¶¶ 167; IPR2020-00088 Petition at 46-47
PO Response at 35-37; IPR2020-00088 Petitioner Reply at 19

Ismagilov 091: Ground 1 Dependent Claims Without Additional Disputes

- Bio-Rad raised no argument regarding the following dependent claims other than those made for the independent claims and 722 Patent dependent Claims 2-3, and so the following dependent claims rise or fall with Claims 2-3
  - 722 Patent Claims: 4-7

IPR2020-00088 PO Response at 35-37
IPR2020-00088 Petitioner Reply at 19

Grounds

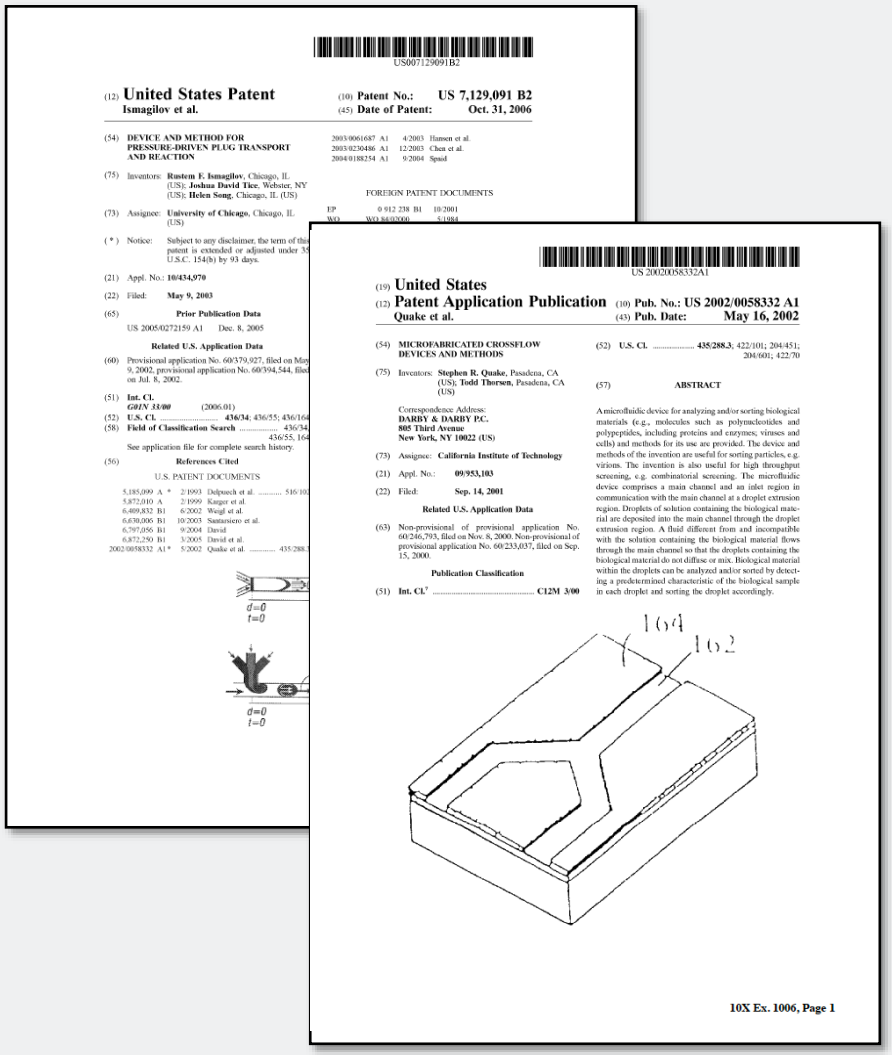
Grounds	References	Claims
1	Ismagilov 091 (§ 102)	837 Patent: 1-2, 4, 10-13, 19-20 722 Patent: 1-7, 10-11, 14
2	Ismagilov 091 and Quake (§ 103)	837 Patent: 1-2, 4, 7, 9-13, 19-20 722 Patent: 1-7, 10-17
3a, 3b	Ismagilov 119 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17
4a, 4b, 5a, 5b	Ismagilov 119 and Pamula 634/238 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17

Claim Constructions

- Grounds 1-2: Bio-Rad's Claim Constructions
- "a" Grounds: 10X's Claim Constructions
- "b" Grounds: Bio-Rad's Claim Constructions

IPR2020-00086 Petition at 23-25; IPR2020-00088 Petition at 22-24

Ismagilov 091 In Combination With Quake Renders The Claims Obvious



US007129091B2

(12) **United States Patent**
Ismagilov et al.

(10) **Patent No.: US 7,129,091 B2**
(45) **Date of Patent: Oct. 31, 2006**

(54) **DEVICE AND METHOD FOR PRESSURE-DRIVEN PLUG TRANSPORT AND REACTION**

(75) Inventors: **Rustem F. Ismagilov**, Chicago, IL (US); **Joshua David Tice**, Webster, NY (US); **Helen Song**, Chicago, IL (US)

(73) Assignee: **University of Chicago**, Chicago, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 93 days.

(21) Appl. No.: **10/434,970**

(22) Filed: **May 9, 2003**

(65) **Prior Publication Data**

US 2005/0272159 A1 Dec. 8, 2005

Related U.S. Application Data

(60) Provisional application No. 60/379,927, filed on May 9, 2002, provisional application No. 60/394,544, filed on Jul. 8, 2002.

(51) **Int. Cl.**
G01N 33/00 (2006.01)

(52) **U.S. Cl.** **436/34**; 436/55; 436/164

(58) **Field of Classification Search** 436/34, 436/55, 164

See application file for complete search history.

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US 20020058332A1

(19) **United States**
(12) **Patent Application Publication**
Quake et al.

(10) **Pub. No.: US 2002/0058332 A1**
(43) **Pub. Date: May 16, 2002**

(54) **MICROFABRICATED CROSSFLOW DEVICES AND METHODS**

(75) Inventors: **Stephen R. Quake**, Pasadena, CA (US); **Todd Thorsen**, Pasadena, CA (US)

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(73) Assignee: **California Institute of Technology**

(21) Appl. No.: **09/953,103**

(22) Filed: **Sep. 14, 2001**

Related U.S. Application Data

(63) Non-provisional of provisional application No. 60/246,793, filed on Nov. 8, 2000. Non-provisional of provisional application No. 60/233,037, filed on Sep. 15, 2000.

Publication Classification

(51) **Int. Cl.**[7] **C12M 3/00**

(52) **U.S. Cl.** **435/288.3**; 422/101; 204/451; 204/601; 422/70

(57) **ABSTRACT**

A microfluidic device for analyzing and/or sorting biological materials (e.g., molecules such as polynucleotides and polypeptides, including proteins and enzymes; viruses and cells) and methods for its use are provided. The device and methods of the invention are useful for sorting particles, e.g. virions. The invention is also useful for high throughput screening, e.g. combinatorial screening. 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. A fluid different from and incompatible with the solution containing the biological material flows through the main channel so that the droplets containing the biological material do not diffuse or mix. Biological material within the droplets can be analyzed and/or sorted by detecting a predetermined characteristic of the biological sample in each droplet and sorting the droplet accordingly.

10X Ex. 1006, Page 1

- Quake expressly discloses the structure of a well in a microfluidic device
- Quake was well known in microfluidics, including droplets
- A person of ordinary skill would have been motivated to combine Ismagilov with the microfluidic device well structures of Quake if additional information on structure was necessary
- The differences between Quake and Ismagilov were minor

IPR2020-00086 Petition at 25-28, 38-40; IPR2020-00088 Petition at 24-26, 38-41

Quake Discloses Wells That Are "upright" / "perpendicular" And "Wider" Than The Channels

837 Claim 1

[1.3] at least one downstream separation chamber comprising a droplet receiving chamber inlet and at least one droplet receiving outlet,

[1.4] wherein the separation chamber is upright to the microchannel and out of the horizontal plane;

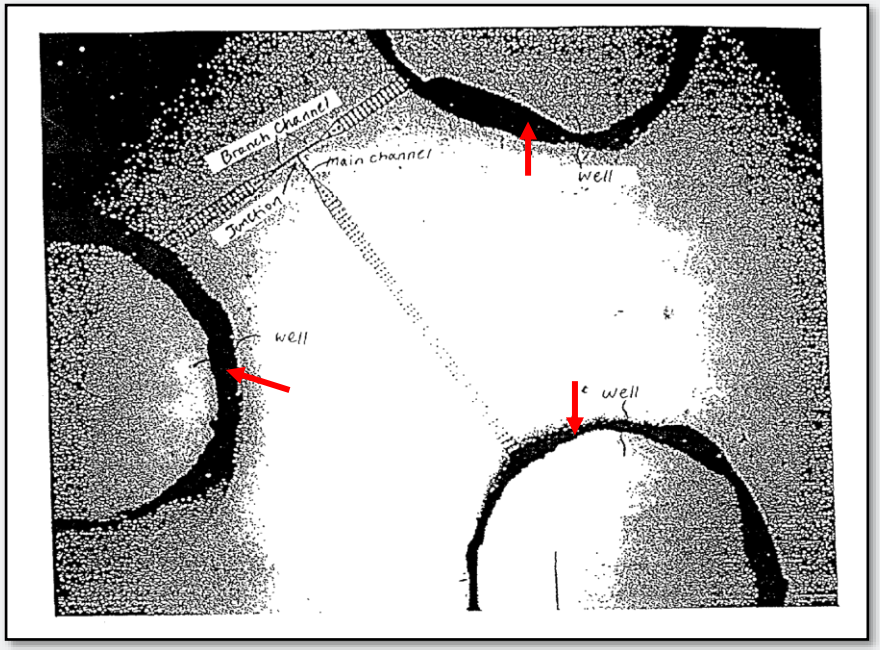
[1.6] wherein the separation chamber has a wider cross-section than the microchannel cross-section to accumulate a plurality of droplets comprising the sample and

722 Claim 1

[1.4] flowing the droplets toward a downstream separation chamber that is in fluidic communication with the main channel,

[1.5] wherein the separation chamber has a wider cross-section than the main channel cross-section and

[1.6] the separation chamber is disposed perpendicular to the main channel; and



Red arrows show wells

IPR2020-00086 Ex. 1006, Fig. 6; IPR2020-00088 Ex. 1006, Fig. 6
IPR2020-00086 Petition at 38-39; IPR2020-00088 Petition at 39-40

Quake Discloses Wells That Are "upright" / "perpendicular" And "Wider" Than The Channels

837 Claim 1

[1.3] at least one downstream separation chamber comprising a droplet receiving chamber inlet and at least one droplet receiving outlet,

[1.4] wherein the separation chamber is upright to the microchannel and out of the horizontal plane;

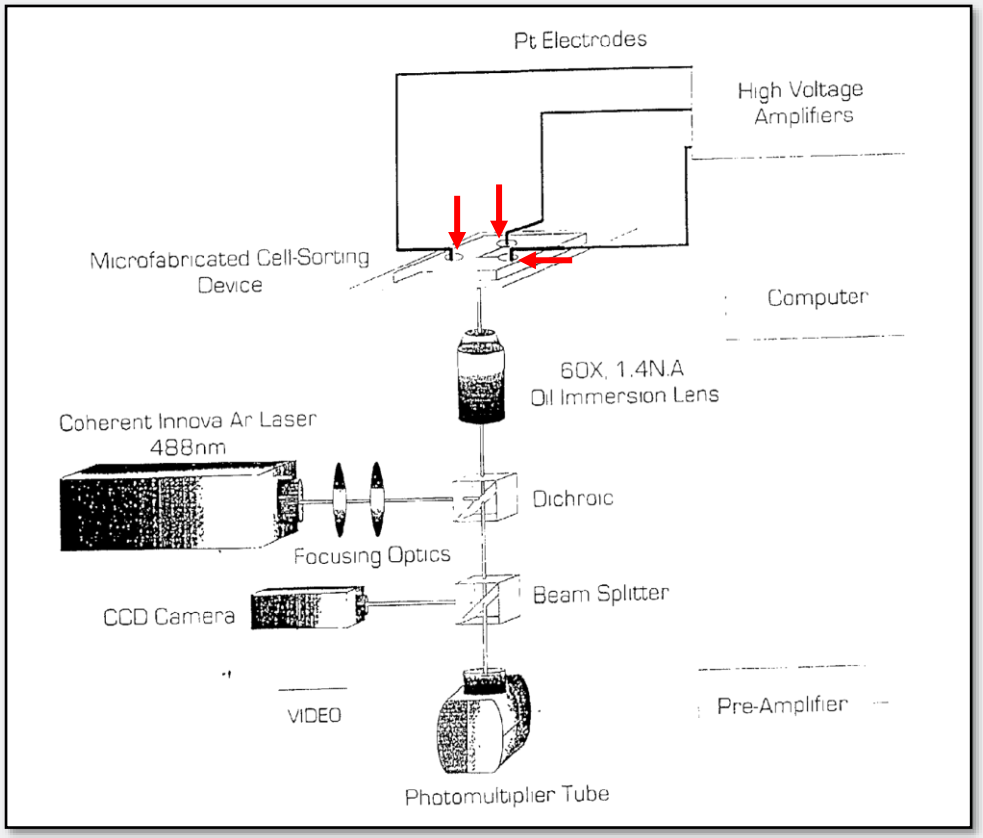
[1.6] wherein the separation chamber has a wider cross-section than the microchannel cross-section to accumulate a plurality of droplets comprising the sample and

722 Claim 1

[1.4] flowing the droplets toward a downstream separation chamber that is in fluidic communication with the main channel,

[1.5] wherein the separation chamber has a wider cross-section than the main channel cross-section and

[1.6] the separation chamber is disposed perpendicular to the main channel; and



Red arrows show wells

IPR2020-00086 Ex. 1006, Fig. 8; IPR2020-00088 Ex. 1006, Fig. 8
IPR2020-00086 Petition at 38-39, 41-42, 45-47; IPR2020-00088 Petition at 39-40, 44-46

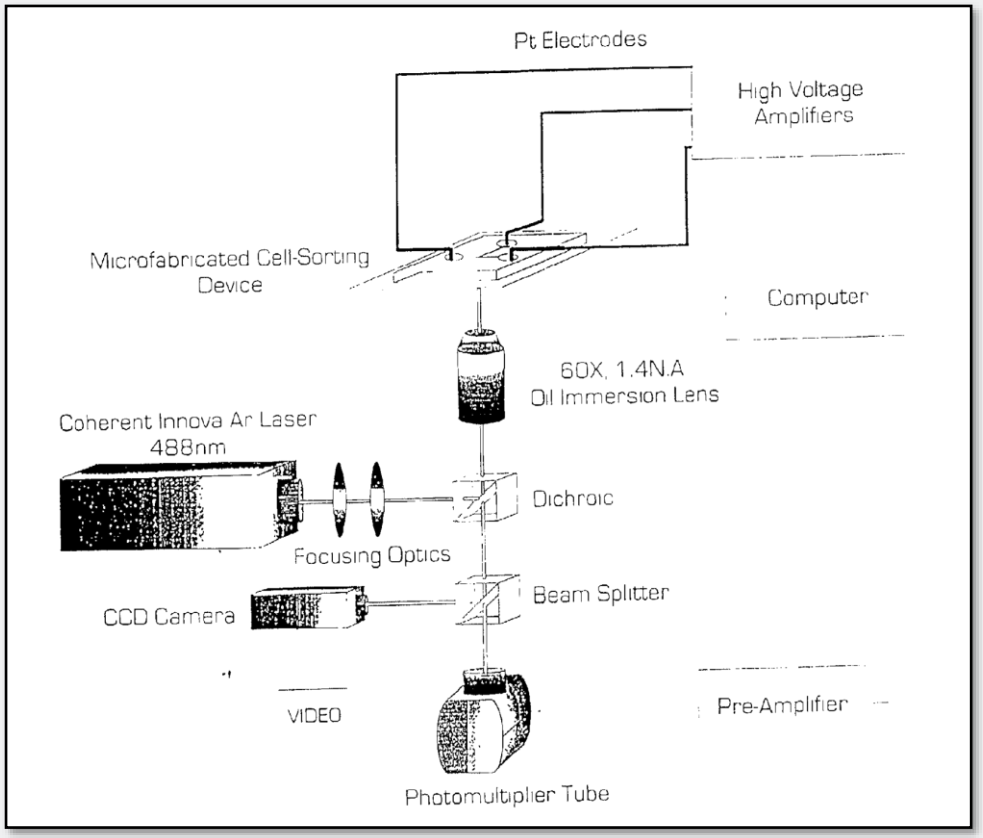
Quake Discloses Wells That Are "upright" / "perpendicular" And "Wider" Than The Channels

837 Claim 1

[1.7] is of a volume sufficient to separate the plurality of droplets comprising the sample from the immiscible fluid within the separation chamber.

722 Claim 1

[1.7] separating the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid.



IPR2020-00086 Ex. 1006, Fig. 8; IPR2020-00088 Ex. 1006, Fig. 8
IPR2020-00086 Petition at 38-39, 41-42, 45-47; IPR2020-00088 Petition at 39-40, 44-46

Ismagilov 091 Discloses A Volume Sufficient To Separate or Separation

- Quake discloses the dimensions of the wells as having a wider cross-section than the channels

indefinitely. 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.

IPR2020-00086 Ex. 1006, ¶ 196; IPR2020-00088 Ex. 1006, ¶ 196
IPR2020-00086 Petition at 41-42; IPR2020-00088 Petition at 42

Ismagilov 091 Discloses A Volume Sufficient To Separate or Separation

Dr. Richard Fair

Duke UNIVERSITY

- Dr. Fair confirmed that the Quake wells extend above the microchannels and were "upright" / "perpendicular"

164. Quake shows wells or reservoirs that have a large volume that extends upright and above the height of the channels. In Quake, the "wells are 2 mm in diameter" and can hold at least 10 to 30 µl of fluid. *Id.*, ¶¶ 196, 200. One microliter (µl) is equal to 1 cubic millimeter, and so the volume of the wells or reservoirs are at least equal to 10 to 30 mm^3. To determine the height of the wells, which are shown in Figure 6 in Quake as cylindrical, the formula for the height of a given cylinder can be used: height = Volume / (π r^2) . The radius of the cylinder is half of the diameter. The equation becomes: height = 10 or 30 mm^3 / (π $(1mm)^2$) . Thus, the height of the cylinder approximating the well would be approximately 3.2 to 9.5 mm. By contrast, the channels in Quake have a depth of only 4 µm. Thus, the well or reservoir in the combination of Quake and Ismagilov 091 extends upward above the plane of the microchannels (and above the glass coverslip). Thus, in the combination

IPR2020-00086 Ex. 1008, ¶ 164; IPR2020-00088 Ex. 1008, ¶ 154
IPR2020-00086 Petition at 41-42; IPR2020-00088 Petition at 42

Ismagilov 091 & Quake: Disputes

- "separation chamber"
- Motivation to combine
- Secondary considerations

IPR2020-00086 Petition at 25-28, 38-40; IPR2020-00088 Petition at 38-53

Ismagilov 091 & Quake Render A "separation chamber" obvious

- Bio-Rad argues that Quake does not disclose separating droplets from immiscible fluid

- Bio-Rad is incorrect
  - The combination takes from Quake the well structure, not the analysis being performed in Quake
  - The droplets in the combination from Ismagilov 091 inherently separate from immiscible fluid as described for Ismagilov 091 alone, and all claim elements under Bio-Rad's reading of the claims are rendered obvious by the combination

IPR2020-00086 PO Response at 48-49; IPR2020-00088 PO Response at 38-53
IPR2020-00086 Petitioner Reply at 21-29; IPR2020-00088 Petitioner Reply at 19-29

Ismagilov 091 & Quake Render A "separation chamber" obvious

- The Board at institution found that Ismagilov 091 in view of Quake taught a "separation chamber"
  - "Patent Owner asserts Quake's paragraphs 198–200 do not disclose "wells intended for separation," as asserted by Petitioner, but rather teach "sorting experiments" where cells can be directed to either side of the T-channels depending upon voltage potential settings." (IPR2020-00088)
  - "Based on the record at this stage of the proceeding, we disagree with Patent Owner's argument. In our view, Petitioner has shown sufficiently that Ismagilov 091 in view of Quake teaches a "separation chamber" under Petitioner's alternative constructions for these terms." (IPR2020-00088)

IPR2020-00088 Institution Decision at 38; *see also* IPR2020-00086 Institution Decision at 38-40

Ismagilov 091 & Quake: Disputes

- "separation chamber"
- Motivation to combine
- Secondary considerations

IPR2020-00086 Petition at 25-28, 38-40; IPR2020-00088 Petition at 38-53

Ismagilov 091 In Combination With Quake Teaches A Separation Chamber

- The Board at institution found that there was a motivation to combine Ismagilov 091 with Quake
  - "[W]e determine that Petitioner's contentions regarding a motivation to combine Ismagilov 091 and Quake include an explanation for how and why a POSA would have combined the cited teachings sufficient to meet the threshold for institution of *inter partes* review. . . . Petitioner is relying on Quake to provide explicit disclosure of structural and functional details, such as the relative dimensions of wells and channels, that Petitioner contends is implicitly or inherently described by Ismagilov 091." (IPR2020-00086)
  - "As support for a motivation to combine, Petitioner cites Ismagilov 091's description of fabrication of channels, substrates, and devices. Pet. 40 (citing Ex. 1004, 16:2–47). That description is similar to Quake's description of fabrication of a microfabricated device that Petitioner relies upon to provide additional details regarding the dimensions and configuration of the wells or reservoirs, their inlets and outlets, and channels. Pet. 38–39, 41–42, 45 (citing Ex. 1006 ¶¶ 196–200, Figs. 6–8)." (IPR2020-00086)

IPR2020-00086 Institution Decision at 38-41; IPR2020-00088 Institution Decision at 38-41

There is Motivation To Combine Ismagilov 091 & Quake

- Bio-Rad argues:
  - Bio-Rad focuses on the Quake description of electrodes instead of pressure-driven flow for droplets

- Bio-Rad is incorrect, and the Board already concluded that the Quake embodiment could be used in a pressure-driven mode
  - "Moreover, at this stage, Patent Owner's argument appears to be inconsistent with Quake's disclosure that the Figure 6 embodiment (with open-topped wells) can be used in a pressure-driven mode."

IPR2020-00086 Institution Decision at 40
IPR2020-00086 PO Sur-Reply at 18; IPR2020-00088 PO Sur-Reply at 18
IPR2020-00086 PO Response at 45-59; IPR2020-00088 PO Response at 38-53
IPR2020-00086 Petitioner Reply at 21-29; IPR2020-00088 Petitioner Reply at 19-29

There is Motivation To Combine Ismagilov 091 & Quake

- Bio-Rad argues:
  - Quake well examples do not relate to droplets and instead relate to sorting cells
- Bio-Rad is incorrect
  - Quake is tilted "Microfabricated Crossflow Devices and Methods," and a person of ordinary skill would look to Quake for its microfluidic structural disclosures (not merely droplet embodiments)
  - Quake disclosures were even copied into Ismagilov
  - The work of the Quake lab in microfluidics was well-known, including based on the work with droplets

IPR2020-00086 Petition at 25-28, 38-40; IPR2020-00088 Petition at 15-16, 24-26, 38-41
IPR2020-00086 PO Sur-Reply at 18; IPR2020-00088 PO Sur-Reply at 18
IPR2020-00086 PO Response at 45-59; IPR2020-00088 PO Response at 38-53
IPR2020-00086 Petitioner Reply at 21-29; IPR2020-00088 Petitioner Reply at 19-29

There is Motivation To Combine Ismagilov 091 & Quake

- Bio-Rad argues:
  - Quake examples including wells relate to sorting cells and do not include droplets

- Bio-Rad is incorrect
  - The same fabrication techniques (cork borers, PDMS molding, and glass cover slips) in Ismagilov 091 and Quake further support the combination (Ismagilov 091, 16:1-47; Quake, ¶¶196, 200, 216)
  - The systems in Quake, including the T-junctions with wells, were disclosed as having multiple applications, including droplets

IPR2020-00086 PO Sur-Reply at 18; IPR2020-00088 PO Sur-Reply at 18
IPR2020-00086 PO Response at 45-59; IPR2020-00088 PO Response at 38-53
IPR2020-00086 Petitioner Reply at 21-29; IPR2020-00088 Petitioner Reply at 19-29

There is Motivation To Combine Ismagilov 091 & Quake

- Quake discloses droplet applications for its systems

[0003] This invention relates to microfluidic devices and methods, including microfabricated, multi-layered elastomeric devices with active pumps and valves. More particularly, the devices and methods of the invention are designed to compartmentalize small droplets of aqueous solution within microfluidic channels filled with oil. The devices and

IPR2020-00086 Ex. 1006, ¶ 3; IPR2020-00088 Ex. 1006, ¶ 3
IPR2020-00086 Petitioner Reply at 24; IPR2020-00088 Petitioner Reply at 2324

There is Motivation To Combine Ismagilov 091 & Quake

- Quake discloses using a similar T-shaped branch with wells to sort water-in-oil droplets in Example 8

to repel the droplet. This effect can be used to sort droplets, in that a focused optical beam can be used to deflect droplets, e.g. from a main channel into a waste or collection channel. Stated another way, a differential in the index of refraction between two phases of a droplet system, e.g. where droplets of one phase are separated or encapsulated by another phase, may be exploited to move or direct droplets in response to radiation pressure. This technique can also be applied to any

IPR2020-00086 Ex. 1006, ¶ 241; IPR2020-00088 Ex. 1006, ¶ 241
IPR2020-00086 Petitioner Reply at 24-25; IPR2020-00088 Petitioner Reply at 24-25

Ismagilov 091 Discloses A Volume Sufficient To Separate or Separation

- Quake discloses using a similar T-shaped branch with wells to sort water-in-oil droplets in Example 8

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. In this example, the hole at the bottom end of the T is used to load the sample. The hole at one arm of the T is used for collecting the sorted sample while the opposite arm is treated as waste. Before use, the PDMS device is placed in a hot bath of HCl to make the surface hydrophilic. The device is then placed onto a No. 1 (150 μm thick) (25×25 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

IPR2020-00086 Ex. 1006, ¶ 216; IPR2020-00088 Ex. 1006, ¶ 216
IPR2020-00086 Petitioner Reply at 24-25; IPR2020-00088 Petitioner Reply at 24-25

Ismagilov 091 & Quake: Disputes

- "separation chamber"
- Motivation to combine
- Secondary considerations

IPR2020-00086 Petition at 25-28, 38-40; IPR2020-00088 Petition at 38-53

Bio-Rad's Secondary Considerations Have Already Been Rejected

- Bio-Rad argued secondary considerations in its Patent Owner Preliminary Response, and the Board rejected that argument

> contributions to the field. Prelim. Resp. 29–34; Exs. 2001–2011, 2013. At this stage, Patent Owner does not direct us to evidence sufficient to show a nexus between Bio-Rad's products and the '837 Patent claims. Patent Owner's naked assertion that Bio-Rad's products "practice" and "embody" the '837 Patent is not sufficient to show nexus. Prelim. Resp. 29, 30. *See, e.g., Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) ("In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a nexus to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention.") (internal quotes omitted); *see also Lectrosonics, Inc. v. Zaxcom, Inc.*, Case IPR2018-01129, Paper 33, at 32 (PTAB Jan. 24, 2020) (precedential) ("For objective indicia of nonobviousness to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.").

IPR2020-00086 Institution Decision at 41-43; IPR2020-00088 Institution Decision at 40-42

Bio-Rad's Response Was Substantially The Same And Equally Deficient

IPR2020-00086 Preliminary Response

Bio-Rad's products, the ddPCR and ddSEQ systems, embody the '837 patent and have been a commercial success, as evident by the high sales volume and revenues generated by Bio-Rad's sales of ddPCR. The inventions disclosed in the '837 patent have contributed to this success. They allow for the utilization of differences in density of the different fluids to concentrate the droplets in a particular part of the chamber. This greatly improved the ability to easily and reliably remove the droplets from the separation chamber while minimizing the removal of unwanted continuous phase fluid. These developments represented a significant improvement on the prior art that greatly advanced the capability of PCR and NGS. (*See, e.g.*, R&D 100 *Archive of Winners* (2012),

IPR2020-00086 Response

Patent Owner's products that embody the '837 patent have also been a commercial success, with the inventions disclosed in the '837 patent contributing to this success. They allow for the utilization of differences in density of the different fluids to concentrate the droplets in a particular part of the chamber. This greatly improved the ability to easily and reliably remove the droplets from the separation chamber while minimizing the removal of unwanted continuous phase fluid. These developments represented a significant improvement on the prior art that greatly advanced the capability of PCR and NGS. (*See, e.g.*, Ex. 2005; Ex. 2006; Ex. 2007; Ex. 2008; Ex. 2009; Ex. 2016 at ¶187).

IPR2020-00086 Petitioner Reply at 28-29; IPR2020-00088 Petitioner Reply at 28-29
IPR2020-00086 PO Response at 53-59; IPR2020-00088 PO Response at 47-53
IPR2020-00086 PO Preliminary Response at 27-34; IPR2020-00088 PO Preliminary Response at 28-35

Bio-Rad's Secondary Considerations Have Already Been Rejected

- Bio-Rad argued secondary considerations in its Patent Owner Preliminary Response, and the Board rejected that argument

> Patent Owner also contends that Petitioner's "products embodying the invention have been a commercial success." Prelim. Resp. 32; Ex. 2012. Again, Patent Owner does not direct us to evidence sufficient to show a nexus between Petitioner's products and the '837 Patent claims.
>
> Patent Owner asserts that "Bio-Rad acquired RainDance and all of its intellectual property in January 2017, including the '837 patent, demonstrating the value that third-parties have placed on acquiring rights to the '837 patent." Prelim. Resp. 34 (citing Ex. 2014). Yet again, Patent Owner does not direct us to evidence sufficient to show a nexus between the '837 Patent claims and Patent Owner's acquisition of RainDance and its intellectual property.

IPR2020-00086 Institution Decision at 41-43; IPR2020-00088 Institution Decision at 40-42

Bio-Rad Did Not Address Information Relevant To The Secondary Considerations Analysis

- Bio-Rad also did **not**
  - Address the many features of the products unrelated to the 837 and 722 Patents and whether those features led to their success/praise/meeting any long-felt need
  - Address that success of 10X's products was determined to be due to 10X's patents
  - Address that its own ddSEQ product is a complete commercial and technological failure

IPR2020-00086 PO Response at 45-59; IPR2020-00088 PO Response at 38-53
IPR2020-00086 Petitioner Reply at 21-29; IPR2020-00088 Petitioner Reply at 19-29

Bio-Rad Did Not Address Information Relevant To The Secondary Considerations Analysis

- Bio-Rad's expert admitted the multiple areas of information she did not address

Q. You have not described in your declaration any analysis of whether the features of 10x's products unrelated to the '837 or '722 patents led to the success of 10x's products.

A. And, again, I would just repeat what I said before that what I have been asked to opine about is specifically about the secondary considerations in light of the '837 and '722 patents. And some of those secondary considerations include the commercial success of both 10x and Bio-Rad's products.

But I, again, was not asked to do a detailed product analysis for either one of those two companies where I would have been able to discuss the relative -- the relevance -- the relative relevance, I guess, of the different features toward the success and the awards and so forth of each one of those products.

What I was asked to do was to think about and opine about secondary considerations in light of these two patents and this set of products.

IPR2020-00086/88 Ex. 1075, 187:14-188:7
IPR2020-00086 Petitioner Reply at 28-29; IPR2020-00088 Petitioner Reply at 28-29

Ismagilov 091 & Quake: Ground 2 Dependent Claims Without Additional Disputes

- Bio-Rad raised no argument regarding the following dependent claims other than those made for the independent claims, and so the following dependent claims rise or fall with the independent claims
  - 837 Patent Claims: 2, 4, 10-13, 19-20
  - 722 Patent Claims: 10-11

IPR2020-00086 PO Response at 49-53; IPR2020-00088 PO Response at 43-46

Ismagilov 091 & Quake: 722 Patents Claims 2/3 Are Obvious

- Bio-Rad disputes that 722 Patent Claims to "collecting the separated droplets" (722 Patent claim 2) / "wherein the separated droplets are collected into a vessel" (722 Patent claim 3) are obvious based on Ismagilov combined with Quake for the same reasons as under Ismagilov Ground 1

- For the same reasons explained in the Ismagilov 091 anticipation section, these claims are rendered obvious

IPR2020-00088 PO Response at 35-36, 43
IPR2020-00088 Petitioner Reply at 19

Ismagilov 091 & Quake: 722 Patents Claims 2/3 Are Obvious

- Ismagilov 091 discloses several applications that require collecting separated droplets in a vessel

high-throughput screening. Highly parallel arrays of microfluidic systems are used for the synthesis of macroscopic quantities of chemical and biological compounds, e.g., the destruction of chemical warfare agents and pharmaceuticals synthesis. Their advantage is improved control over mass

Using the above devices and techniques, a variety of reactions can be conducted, including polymerizations, crystallizations (including small molecule and proteins), nanoparticle synthesis, formation of unstable intermediates, enzyme-catalyzed reactions and assays, protein—protein binding, etc. More than one reaction can be conducted,

The devices and methods according to the present invention may also be used for synthesizing polymers. Since the

Ismagilov 091 (IPR2020-00088 Ex. 1004), 1:24-28, 3:36-41, 50:51-52

IPR2020-00088 Petition at 46-47; IPR2020-00088 PO Response at 35-37; IPR2020-00088 Petitioner Reply at 19

Ismagilov 091 & Quake: 722 Patents Claims 2/3 Are Obvious

Dr. Richard Fair

Duke UNIVERSITY

- Dr. Fair explained that the purpose of collecting droplets by micropipette is to transfer them

1:24-28, 3:36-41, 50:51-52. Indeed, the purpose of collecting droplets by micropipette will be to then transfer the droplets and collect them in a suitable vessel suitable for such collection.

IPR2020-00088 Ex. 1008, ¶¶ 167; IPR2020-00088 Petition at 46-47
IPR2020-00088 Petitioner Reply at 19

Ismagilov 091 & Quake: Ground 2 Dependent Claims Without Additional Disputes

- Bio-Rad raised no argument regarding the following dependent claims other than those made for the independent claims and 722 Patent dependent Claims 2-3, and so the following dependent claims rise or fall with Claims 2-3
  - 722 Patent Claims: 4-7

IPR2020-00088 PO Response at 35-37
IPR2020-00088 Petitioner Reply at 19

Ismagilov 091 & Quake: 837 Patent Claims 7/9 Are Obvious

- Bio-Rad disputes that 837 Patent Claims to "droplet receiving outlet is coupled to a vessel" (837 Patent Claim 7) / "the vessel is a PCR tube or a test tube" (837 Patent Claim 9) are obvious based on Ismagilov combined with Quake
  - Bio-Rad argues that the droplet receiving outlet is not disclosed as coupled to a vessel

IPR2020-00086 PO Response at 50-51
IPR2020-00086 Petitioner Reply at 26-27

Ismagilov 091 & Quake: 837 Patent Claims 7/9 Are Obvious

- Ismagilov 091 renders obvious transferring droplets collected by micropipette to another vessel
  - Ismagilov discloses both collection by micropipette and sample tube

> the flow of solution to an outlet. The outlet can be adapted for receiving, for example, a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube. Collection can also be done using micropipettes.

  - Droplets collected by micropipette would be transferred to another vessel for downstream use, and such vessels were known, as Ismagilov describes a 1.5 ml centrifuge tube
  - The droplets would not be collected by micropipette and thrown away, and so the operable link by pipette, as Bio-Rad accused of infringement, was obvious

Ismagilov 091 (IPR2020-00086 Ex. 1004), 17:27-30; IPR2020-00086 Petition at 47-48
IPR2020-00086 Petitioner Reply at 26-27

Ismagilov 091 & Quake: 722 Patent Claims 12/13 Are Obvious

- Bio-Rad disputes that 722 Patent Claims to "the biological material further comprises one or more labels" (dependent claim 12) / "wherein the one or more labels are DNA tags, dyes, quantum dot, or combination thereof" (722 Patent Claim 13) are obvious based on Ismagilov combined with Quake
  - Bio-Rad argues that there is no basis to combine Ismagilov and Quake labels

IPR2020-00088 PO Response at 35-36, 45-46
IPR2020-00088 Petitioner Reply at 19, 25-27

Ismagilov 091 & Quake: 722 Patent Claims 12/13 Are Obvious

- Ismagilov 091 discloses sorting biological molecules, including cells

chemical reactivity catalyzed by an enzyme). Biological particles or molecules such as cells and virions can be sorted according to whether they contain or produce a particular protein, by using an optical detector to examine each cell or virion for an optical indication of the presence or amount of that protein. A chemical itself may be detectable, for

Ismagilov 091 (IPR2020-00088 Ex. 1004), 31:35-40; IPR2020-00088 Petition at 50-51
IPR2020-00086 Petitioner Reply at 25-26

Ismagilov 091 & Quake: 722 Patent Claims 12/13 Are Obvious

- The Ismagilov 091 general labeling was obvious to combine with the specific labeling of cells described in Quake

[0165] In one embodiment the signal is in the form of a marker that associates within or binds to a particular cell type. The signal therefore acts to identify the cell as having a particular characteristic, e.g., a protein (receptor) or saccharride, such that the reporter signal from a given cell is proportional to the amount of a particular characteristic. For example, the reporter may be an antibody, a receptor or a ligand to a receptor (which bind to a protein or sugar), or a fragment thereof, each having a detectable moiety, such as a dye that fluoresces. The reporter can bind to a structure on

Quake (IPR2020-00088 Ex. 1006), ¶ 165; IPR2020-00088 Petition at 50-51
IPR2020-00088 Petitioner Reply at 25-26

Ismagilov 091 & Quake: 722 Patent Claims 15-17 Are Obvious

- Bio-Rad disputes that the following 722 Patent Claims are obvious based on Ismagilov and Quake:
  - "placing the droplets onto a second continuous phase carrier fluid" (dependent claim 15)
  - "wherein the second continuous phase carrier fluid comprises a de-stabilizing surfactant" (dependent claim 16)
  - "after the placing step, further comprising destabilizing the droplets" (dependent claim 17)

  - Bio-Rad argues there is no motivation to combine Ismagilov and Quake
  - Bio-Rad is incorrect: Ismagilov 091 disclosures render the additional limitations of these claims obvious and Bio-Rad identifies nothing substantively lacking

IPR2020-00088 PO Response at 35-36, 45-46
IPR2020-00088 Petitioner Reply at 19, 25-27

Ismagilov 091 & Quake: 722 Patent Claims 15-17 Are Obvious

- Ismagilov 091 disclosed 1H,1H,2H,2H-perfluorooctanol for droplet merging, and a second continuous carrier using such a destabilizing surfactant was obvious to result in merging (i.e., breaking) multiple droplets

2H-perfluorooctanol (98%, Alfa-Aesar). The experiments were typically performed using 10:1 mixtures of perfluoro-decaline and 1H,1H,2H,2H-perfluorooctanol.

Ismagilov 091 (IPR2020-00088 Ex. 1004), 61:19-21; IPR2020-00088 Petition at 51-53
IPR2020-00088 Petitioner Reply at 26-27

Ismagilov 091 & Quake: 722 Patent Claims 15-17 Are Obvious

- Ismagilov 091 discloses several applications that require collecting separated droplets in a vessel

high-throughput screening. Highly parallel arrays of microfluidic systems are used for the synthesis of macroscopic quantities of chemical and biological compounds, e.g., the destruction of chemical warfare agents and pharmaceuticals synthesis. Their advantage is improved control over mass

Using the above devices and techniques, a variety of reactions can be conducted, including polymerizations, crystallizations (including small molecule and proteins), nanoparticle synthesis, formation of unstable intermediates, enzyme-catalyzed reactions and assays, protein—protein binding, etc. More than one reaction can be conducted,

The devices and methods according to the present invention may also be used for synthesizing polymers. Since the

Ismagilov 091 (IPR2020-00088 Ex. 1004), 1:24-28, 3:36-41, 50:51-52; IPR2020-00088 Petition at 51-53
IPR2020-00088 Petitioner Reply at 26-27

Ismagilov 091 & Quake: 722 Patent Claims 15-17 Are Obvious

- Ismagilov 091 disclosed a biocompatible fluorosurfactant

> Fluorosurfactants terminated with OEG-groups have been shown to demonstrate biocompatibility in blood substitutes and other biomedical applications. Preferably, oil-soluble

> specific protein adsorption will also be characterized. FIG. **24** shows examples of fluorinated surfactants that form monolayers that are: resistant to protein adsorption; positively charged; and negatively charged. For OEG-terminated

Ismagilov 091 (IPR2020-00088 Ex. 1004), 37:23-35; IPR2020-00088 Petition at 51-53
IPR2020-00088 Petitioner Reply at 26-27

Ismagilov 091 & Quake: 722 Patent Claims 15-17 Are Obvious

- A person of ordinary skill would have looked to known methods of demulsification, which included surfactant demulsifiers and fatty alcohols

Encyclopedic Handbook of Emulsion Technology

Chemicals used as demulsifiers may be simple surfactants. These may be cationic such as quaternary

IPR2020-00088 Ex. 1009, 127-28, Table 4; IPR2020-00088 Petition at 11, 51-53
IPR2020-00088 Petitioner Reply at 26-27

Grounds

Grounds	References	Claims
1	Ismagilov 091 (§ 102)	837 Patent: 1-2, 4, 10-13, 19-20 722 Patent: 1-7, 10-11, 14
2	Ismagilov 091 and Quake (§ 103)	837 Patent: 1-2, 4, 7, 9-13, 19-20 722 Patent: 1-7, 10-17
3a, 3b	Ismagilov 119 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17
4a, 4b, 5a, 5b	Ismagilov 119 and Pamula 634/238 (§ 103)	837 Patent: 1-4, 7-13, 19-20 722 Patent: 1-7, 10-11, 14-17

Claim Constructions

- Grounds 1-2: Bio-Rad's Claim Constructions
- "a" Grounds: 10X's Claim Constructions
- "b" Grounds: Bio-Rad's Claim Constructions

IPR2020-00086 Petition at 23-25; IPR2020-00088 Petition at 22-24

Ismagilov 119 and Pamula: Disputes

- Claim Construction
- Ismagilov 119 (3a, 3b)
- Ismagilov 119/Pamula (4a, 4b, 5a, 5b)

IPR2020-00086 Institution Decision at 43-52; Petition at 56-71; PO Response at 59-61; Petitioner Reply at 27-28
IPR2020-00088 Institution Decision at 43-45; Petition at 53-69; PO Response at 53-54; Petitioner Reply at 27-28

Claim Construction: 10X's Constructions Are Narrower In Relevant Respect Than Bio-Rad's

Term or Phrase	Bio-Rad's Constructions	10X's Proposed Construction
"separation chamber" (837 Patent, Claim 1; 722 Patent, Claims 1, 14)	*Contentions:* Broad enough to encompass an open well *Proposed:* "chamber sized to accommodate multiple droplets and an immiscible fluid in separated form"	"a space that is substantially enclosed"
"droplet receiving outlet" (837 Patent, Claim 1)	*Contentions:* Broad enough to include the opening at the top of an open outlet well *Proposed:* "portion of the separation chamber where droplets are collected"	*Subject to 112(f):* *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 *Function:* receiving substantially only droplets when exiting from the chamber *Alternative:* "a structure connected to the interior space of the chamber and configured so that substantially only droplets flow into it when exiting the chamber"

IPR2020-00086 Petition at 18-19; IPR2020-00088 Petition at 19
IPR2020-00086 PO Response at 18-25; IPR2020-00088 PO Response at 18-21

Ismagilov 119 and Pamula: Claim Construction Was Sufficiently Addressed

- Grounds 3b, 4b, 5b were under Bio-Rad's constructions
  - Bio-Rad argues:
    - The Institution Decision correctly found that the Petition did not sufficiently apply Bio-Rad's construction
  - 10X respectfully disagrees:
    - 10X explained in the Petition, and Bio-Rad does not dispute, that 10X's constructions were narrower than Bio-Rad's constructions
    - 10X cited Dr. Fair's confirmation that 10X's constructions are narrower than Bio-Rad's (IPR2020-00086 Petition at 56; IPR2020-00088 Petition at 53)
    - Bio-Rad's expert confirmed that 10X's constructions are narrower than Bio-Rad's
    - Therefore any prior art that meets 10X's narrow constructions necessarily also meets Bio-Rad's broader construction
    - No other proof is necessary

IPR2020-00086 Institution Decision at 43-52; Petition at 56-71; PO Response at 59-61; Petitioner Reply at 27-28
IPR2020-00088 Institution Decision at 43-45; Petition at 53-69; PO Response at 53-54; Petitioner Reply at 27-28

Ismagilov 119 and Pamula: Bio-Rad's Constructions Are Broader Than 10X's Constructions

- Bio-Rad's expert admitted Bio-Rad's "separation chamber" construction was broader than 10X's construction

Q. Your construction of separation chamber includes substantially enclosed spaces; correct?

A. I don't think that's what I've said. I said the claim term separation chamber means a chamber sized to accommodate multiple droplets in an immiscible fluid in separated form.

Q. My question is not what you're proposing as the construction, but whether your proposed construction is broad enough to include substantially enclosed spaces?

A. Well, again, my construction simply says that this -- there needs to be a chamber sized to accommodate multiple droplets in an immiscible fluid in separated form. The construction doesn't say anything about enclosed or not enclosed.

Q. So your construction would cover either enclosed or open structures?

A. As long as it's a chamber sized to accommodate multiple droplets in an immiscible fluid in separated form.

IPR2020-00086/88 Ex. 1075, 145:7-146:1, 153:2-15
IPR2020-00086 Petitioner Reply at 2-3; IPR2020-00088 Petitioner Reply at 1-2

Ismagilov 119 and Pamula: Bio-Rad's Constructions Are Broader Than 10X's Constructions

- Bio-Rad's expert admitted "droplet receiving outlet" construction was broader than 10X's construction

Q. So let me break it down and see if that helps. So your construction doesn't require that the droplet receiving outlets collect substantially only droplets.

A. Well, I think again the '837 specification discusses that, but I've just said in paragraph 97 that we can construe the droplet receiving outlet as a portion of the separation chamber where droplets are collected.

Q. So I'm trying to understand your answer there. And so when you're saying what should be the construction of droplet receiving outlet, that doesn't require that substantially only droplets be collected; correct?

A. Well, again, I've said that in my opinion the claim term "droplet receiving outlet" should be construed just as a portion of the separation chamber where droplets are collected.

And then again I've pointed out that the '837 specification in one place describes that as an outlet that's positioned to receive substantially only the partitioned portions of the sample. And so that would be included in that definition.

IPR2020-00086/88 Ex. 1075, 145:22-146:1, 152:18-153:15
IPR2020-00086 Petitioner Reply at 2-3; IPR2020-00088 Petitioner Reply at 1-2

Ismagilov 119 and Pamula: Disputes

- Claim Construction
- Ismagilov 119 (3a, 3b)
- Ismagilov 119/Pamula (4a, 4b, 5a, 5b)

IPR2020-00086 Institution Decision at 43-51; Petition at 56-71; PO Response at 59-61; Petitioner Reply at 27-28
IPR2020-00088 Institution Decision at 43-45; Petition at 53-69; PO Response at 53-54; Petitioner Reply at 27-28

Ismagilov 119 Renders A Density Sorter Obvious

- Ismagilov 119 (3a, 3b)
  - Bio-Rad argues:
    - The Institution Decision correctly found that Ismagilov 119 discloses sorting plugs from each other based on their relative density, not sorting droplets from the immiscible fluid
  - 10X respectfully disagrees:
    - Ismagilov refers to a singular "density," not multiple densities
    - Under either interpretation, the same separation chamber structure is required and obvious to a person of ordinary skill

IPR2020-00086 Institution Decision at 43-51; Petition at 56-71; PO Response at 59-61; Petitioner Reply at 27-28
IPR2020-00088 Institution Decision at 43-45; Petition at 53-69; PO Response at 53-54; Petitioner Reply at 27-28

Ismagilov 119 Renders A Density Sorter Obvious

[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.

Ismagilov 119 (IPR2020-00086 & IPR2020-00088 Ex. 1005), ¶ 123
IPR2020-00086 Petition at 57; IPR2020-00088 Petition at 56

Ismagilov 119 Renders A Density Sorter Obvious

- Regardless of whether droplets are being separated from immiscible fluid or droplets of different densities are separated from each other, a person of ordinary skill in the art would have known:
  a) density-based sorting relies on the vertical force of gravity
  b) any density-based sorting takes time and space for the droplets to move through the oil, and it was known the droplets in a large vessel sink or float based on density
  c) sorting is pointless without collection, 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.
- Based on that, a person of ordinary skill would have known to build an (a) "upright" / "perpendicular" chamber (b) wider than the channels with (c) an outlet for collecting the droplets

IPR2020-00086 Institution Decision at 43-52; Petition at 8-12, 56-71; PO Response at 59-61; Petitioner Reply at 27-28
IPR2020-00088 Institution Decision at 43-45; Petition at 8-13, 53-69; PO Response at 53-54; Petitioner Reply at 27-28

Ismagilov 119 and Pamula: Disputes

- Claim Construction
- Ismagilov 119 (3a, 3b)
- Ismagilov 119/Pamula (4a, 4b, 5a, 5b)

IPR2020-00086 Institution Decision at 43-52; Petition at 56-71; PO Response at 59-61; Petitioner Reply at 27-28
IPR2020-00088 Institution Decision at 43-45; Petition at 53-69; PO Response at 53-54; Petitioner Reply at 27-28

Ismagilov 119 and Pamula Render A Density Sorter Obvious

- Ismagilov 119/Pamula (4a, 4b, 5a, 5b)
  - Bio-Rad argues:
    - The Institution Decision correctly found the Petition did not sufficiently explain how and why a person of ordinary skill would have combined Ismagilov 119 with Pamula
  - 10X:
    - Pamula teaches a device that operates based on the difference in density between the droplets and oil, which is what Ismagilov 119 indisputably refers to
    - For any additional structural details regarding a density sorter, a person of ordinary skill would look to the structure described in Pamula
    - Regardless of the interpretation of Ismagilov 119, there would have been a motivation to combine the Ismagilov 119 density sorter with the Pamula density sorter
    - Dr. Fair, one of the Pamula inventors, explained how the Ismagilov and Pamula systems would be combined by a person of ordinary skill (IPR2020-00086 Ex. 1008, ¶ 155-59, IPR2020-00086 Ex. 1008, ¶ 155-59)

IPR2020-00086 Institution Decision at 43-52; Petition at 56-71; PO Response at 59-61; Petitioner Reply at 27-28
IPR2020-00088 Institution Decision at 43-45; Petition at 53-69; PO Response at 53-54; Petitioner Reply at 27-28

Pamula Has A Separation Chamber

[0418] The filler fluid may be selected to have a particular density relative to the droplet phase. A difference in density between the two phases can be used to control or exploit buoyancy forces acting upon the droplets. Examples of two-phase systems useful in this aspect of the invention include water/silicone oil, water/flourinert, and water/fluorosilicone oil. When one phase is buoyant, then that effect can be exploited in a vertical configuration as a means to transport one phase through the other. For example, a waste or collection well can exist at the top or bottom of the droplet microactuator where droplets are delivered to that reservoir by simply releasing them at an appropriate point and allowing them to float or sink to the target destination. Such an

Pamula 634 (IPR2020-00086/88 Ex. 1007), ¶ 418; *see also* Pamula 238 (IPR2020-00086/88Ex. 1018), ¶ 418
IPR2020-00086 Petition at 61; IPR2020-00088 Petition at 61

Ismagilov 119 & Ismagilov 119/Pamula: 837 Patent Claim 8 Is Obvious

- 837 Patent Claim 8: "The assembly of claim 7, wherein the droplet receiving outlet is sealably coupled to a vessel."
  - Ismagilov 091 discloses an outlet that receives a sample tube

> the flow of solution to an outlet. The outlet can be adapted for receiving, for example, a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube. Collection can also be done using micropipettes.

  - It was well known that creamed emulsions were collected (IPR2020-00086 Ex. 1012 at 47-48)
  - It was obvious to combine an outlet that receives a tube with the outlet of the density sorter and obvious to try it as one of the limited options

IPR2020-00086 Petition at 8-12, 68-69
Ismagilov 091 (IPR2020-00086 Ex. 1004), 17:27-30

Ismagilov 119 & Ismagilov 119/Pamula: 837 Patent Claim 8 Is Obvious

- The Examiner confirmed it would have been obvious to use a tube as a vessel

> Regarding claim 9, Lee et al. inherently teach a test tube (¶ 0030, 0096+). In the event that the PCR tube or a test tube is not shown with sufficient specificity, then it would have been obvious to one having ordinary skill in the art to use a test tube or a PCR tube as the vessel, as the claimed improvement on a device or apparatus is no more than "the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for improvement," and therefore the claim is unpatentable under 35 U.S.C. 103(a). Ex

- Pamula further describes delivery of the sorted droplets to a collection well, and the choice of a sample tube as a vessel was obvious and a simple substitution

IPR2020-00086 Petition at 8-12, 68-69
IPR2020-00086 Ex. 1002, 1099-1100

Ismagilov 119/Pamula: 837 Patent Claim 8 Is Obvious

- 837 Patent Claim 3: "The assembly of claim 1, wherein the at least one droplet receiving outlet is located on the lower portion of the separation chamber."
  - Ismagilov 119 and Pamula render this obvious
  - Pamula discloses a collection well at the bottom of the vertical density sorting structure
  - The bottom of the chamber was an obvious place to locate the outlet for sorting droplets denser than the immiscible fluid

IPR2020-00086 Petition at 67

Ismagilov 119 & Ismagilov 119/Pamula: Additional Reasons 837 Patent Claims Are Obvious

- Claim 4: "outlet is located on the upper portion of the separation chamber"
  - Obvious to include the outlet on the upper portion of the separation chamber in Ismagilov 119 as described
- Claims 7 & 9: "the droplet receiving outlet is coupled to a vessel" / "the vessel is a PCR tube or a test tube"
  - Similar reasoning as for Claim 8
- Claim 10: "the droplet receiving outlet receives substantially one or more droplets"
  - Same reasoning as for the outlet receiving substantially only droplets
- Claim 19: "sorting module"
  - Ismagilov contemplates multiple sorters, and it could be included

IPR2020-00086 Petition at 67-71

Ismagilov 119 & Ismagilov 119/Pamula: Additional Reasons 722 Patent Claims Are Obvious

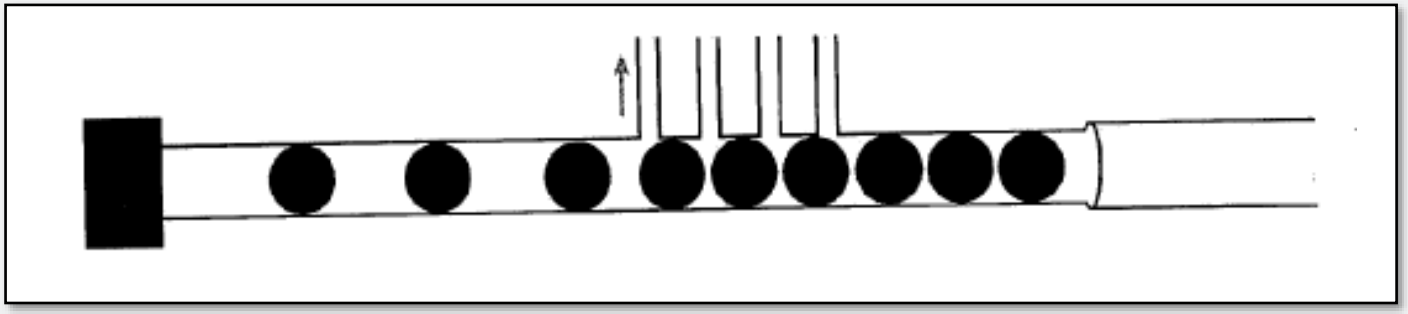
- Claim 2-4: "collecting the separated droplets" / "in a vessel" / "wherein the vessel is a PCR tube or test tube"
  - Sorted droplets have little immiscible fluid between them, the purpose of generating that fraction is to collect it, and it was obvious to use a tube based on Ismagilov 091's disclosure of a centrifuge tube

IPR2020-00088 Petition at 66-69

Ismagilov 119 & Ismagilov 119/Pamula: Additional Reasons 722 Patent Claims Are Obvious

- Claims 15-17: "placing the droplets onto a second continuous phase carrier fluid" / "de-stabilizing surfactant" / "after the placing step, further comprising destabilizing the droplets"
- Ismagilov 119 discloses adding a second continuous phase, and it would have been obvious to add a second continuous carrier phase through branch channels and destabilize with perfluorooctanol as described earlier

increases. Carrier can be replaced using this design by having one side branch channel removing carrier, and another side branch channel adding another carrier.



IPR2020-00088 Petition at 66-69
(IPR2020-00086 Ex. 1005), ¶ 128, Fig. 7

ISMAGILOV GROUNDS
END