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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.

Petitioner,

v.

BIO-RAD LABORATORIES, INC.

Patent Owner.

IPR2018-00300

U.S. Patent No. 9,216,392

PETITION FOR *INTER PARTES* REVIEW

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- 1002 Prosecution history of U.S. Patent No. 9,216,392 (U.S. Patent Application No. 12/962,507)
- 1003 Declaration of Dr. Khushroo Gandhi
- 1004 U.S. Published Application 2010/0184928 A1 to Kumacheva et al.
- 1005 U.S. Published Application 2005/0266582 A1 to Modlin et al.
- 1006 Duffy, et al., *Rapid Prototyping of Microfluidic Systems in Poly(dimethylsiloxane)*, Anal. Chem., 70:4974-84 (1998)
- 1007 Chien and Parce, *Multiport flow-control system for lab-on-a-chip microfluidic devices*, J. Anal. Chem., 371-106-11 (2001)
- 1008 U.S. Published Application 2009/0269248 to Falb, et al.
- 1009 U.S. Published Application 2009/0047713 to Handique
- 1010 U.S. Published Application 2009/0035770 to Mathies
- 1011 U.S. Provisional Application 61/047,377 to Falb et al.
- 1012 U.S. Patent No. 6,123,798 to Gandhi et al.
- 1013 Publication information for Anna, et al., *Formation of dispersions using “flow focusing” in microchannels*, Appl. Phys. Lett., 82(3):364-66 (2003)
- 1014 U.S. Published Application 2002/0058332 to Quake et al.

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- 1016 Anna, et al., *Formation of dispersions using “flow focusing” in microchannels*, Appl. Phys. Lett., 82(3):364-66 (2003)
- 1017 U.S. Provisional Application 60/924,921 to Kumacheva
- 1018 U.S. Published Application 2008/0166720 to Hsieh, et al.
- 1019 U.S. Published Application 2007/0166200 to Zhou, et al.
- 1020 U.S. Published Application 2008/0038810 to Pollack et al.
- 1021 U.S. Published Application 2010/0022680 to Karnik, et al.
- 1022 U.S. Published Application 2009/0012187 to Chu, et al.
- 1023 Galambos, et al., *Precision Alignment Packaging for Microsystems with Multiple Fluid Connections*, Proceedings of 2001 ASME: International Mechanical Engineering Conference and Exposition, November 11-16, 2001. p. 1-8
- 1024 Publication information for Nisisako and Torii, *Microfluidic large-scale integration on a chip for mass production of monodisperse droplets and particles*, Lab on a Chip, 8:287-93 (2008)
- 1025 Li and Li, Microfluidic Lab-on-a-Chip (Book Chapter), p. 581-679 (2005)
- 1026 Whitesides and Strook, *Flexible Methods for Microfluidics, Physics Today*, June 2001: 42-48

- 1027 Complainants' Ground Rule 4 Disclosures, Certain Microfluidic Devices,
USITC Inv. No. 337-TA-1068, filed November 17, 2017
- 1028 U.S. Patent No 6,176,962 to Soane
- 1029 U.S. Published Application 2008/0056948 A1 to Dale and Knight
- 1030 Publication information for Kawai, et al., *Mass-Production System of
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- 1031 Nisisako and Torii, *Microfluidic large-scale integration on a chip for
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- 1032 Publication information for Duffy, et al., *Rapid Prototyping of
Microfluidic Systems in Poly(dimethylsiloxane)*, Anal. Chem., 70:4974-
84 (1998)
- 1033 Bernouilli Pressure Lowering, <http://hyperphysics> p. 1-4
- 1034 Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain
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- 1035 Publication information for Chien and Parce, *Multiport flow-control
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- 1036 Definition of Gasket, Merriam-Webster
- 1037 Kawai, et al., *Mass-Production System of Nearly Monodisperse Diameter Gel Particles Using Droplets formation in a Microchannel, Micro Total Analysis Systems*, Micro Total Analysis Systems, 1:368-70 (2002)
- 1038 Publication information for Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain Reaction in Picoliter Droplets*, Anal. Chem. 2007, 79, 8471-8475
- 1039 U.S. Patent No. 6,915,679 to Chien et al.
- 1040 Publication information for Li and Li, Microfluidic Lab-on-a-Chip (Book Chapter), p. 581-679 (2005)
- 1041 Becker and Gartner, *Polymer microfabrication technologies for microfluidic systems*, Anal. Bioanal. Chem, 390:89-111
- 1042 Publication information for Becker and Gartner, *Polymer microfabrication technologies for microfluidic systems*, Anal. Bioanal. Chem, 390:89-111
- 1043 de Mello and Manz, *Chip technology for micro-separation*, BioMethods 10:129-177 (1999)
- 1044 U.S. Published Application No. 2004/0109793 to McNeely, et al.
- 1045 *Curriculum Vitae* of Dr. Khushroo Gandhi
- 1046 UK Patent Application No. 2097692 to Shaw Stewart

- 1047 Mair, et al., *Injection molded microfluidic chips featuring integrated
interconnects, Lab on a Chip*, 6:1346-54 (2006)
- 1048 Publication information for Mair, et al., *Injection molded microfluidic
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- 1049 Declaration of Ruth G. Davila
- 1050 U.S. Patent No. 9,126,160 to Ness et al.

I. INTRODUCTION

Petitioner, 10X Genomics, Inc. (“Petitioner”) respectfully requests *inter partes* review (“IPR”) of claims 1-21 of U.S. Patent No. 9,216,392 (“the ’392 Patent”, Ex. 1001). For the reasons set forth below, each of the challenged claims is invalid.

II. MANDATORY NOTICES

A. Real Party-in-Interest

10X Genomics, Inc. is the real party-in-interest.

B. Related Matters

Petitioner is contemporaneously filing two additional *inter partes* review petitions challenging claims 1-21 of the ‘392 patent (IPR2018-00301 and IPR2018-00302). The following other proceedings would affect or be affected by a decision in this proceeding: *Bio-Rad Laboratories, Inc., et al. v. 10X Genomics, Inc.*, Case No. 3:17-CV-4339 (N.D. Cal.) and Re: Certain Microfluidic Devices, Investigation Number 337-TA-1068 (ITC).

C. Designation of Counsel

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D. Service Information

Pursuant to 37 C.F.R. § 42.10(b), Powers of Attorney accompany this Petition. Please address all correspondence to lead counsel. Petitioner consents to service of all documents via the following email addresses:

ggardella@gardellagrace.com, ddevore@convergentlaw.com and docketing@gardellagrace.com.

E. Fees

The undersigned authorizes the PTO to charge the fee set forth in 37 C.F.R. § 42.15(a) for this Petition to Deposit Account No. 601484. The undersigned authorizes payment for additional fees that may be due with this petition to be charged to the above-referenced Deposit Account.

III. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

IV. OVERVIEW OF CHALLENGE AND RELIEF REQUESTED

Pursuant to Rules 42.22(a)(1) and 42.104(b)(1)-(2), Petitioner challenges claims 1-21 (“the challenged claims”) of the ’392 Patent and requests that each challenged claim be canceled on the basis that the subject matter is obvious under pre-AIA 35 U.S.C. §103(a).

A. Grounds for Challenge

This petition, together with the support exhibits including the declaration of Khushroo Gandhi, Ph.D. (“Gandhi Declaration,” Ex. 1003), demonstrates that there is a reasonable likelihood that at least one of the challenged claims is unpatentable for the reasons set forth herein. 35 U.S.C. §314(a).

B. Prior Art Patents and Printed Publications Relied Upon

Petitioner relies upon the following patents and printed publications, the majority of which were before the Examiner during *ex parte* prosecution.

1. U.S. Published Application 2010/0184928 A1 to Kumacheva

U.S. Published Application 2010/0184928 A1 to Kumacheva

(“Kumacheva,” Ex. 1004), filed on June 5, 2008 and published on July 22, 2010, is prior art to the ’392 patent under 35 U.S.C. §102 (e) because it was filed before the earliest claimed priority date, September 23, 2008. Kumacheva was not before the Examiner during prosecution.

Kumacheva claims benefit to U.S. Provisional Application serial no. 60/924,921 filed on June 5, 2007. (Ex. 1017.) Even if the ruling of *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015) is extended to published applications (which it should not be), Kumacheva is prior art at least as of June 5, 2007 because the provisional application supports the claims of the Kumacheva ‘928 publication. The Kumacheva provisional (Ex. 1017) supports, for instance, claim 1 of the ‘928 published application. (Ex. 1003 ¶39.) Claim 1 of the ‘928 application is included verbatim in the specification of the provisional application and the provisional application also sets forth additional

disclosure which independently supports each element of that claim. (Ex. 1017 pp. 16-18, 30-31¹; Ex. 1003 ¶39.) (*Id.*)

2. U.S. Published Application 2005/0266582 A1 to Modlin et al.

U.S. Published Application 2005/0266582 A1 to Modlin et al. (“Modlin,” Ex. 1005), filed on April 14, 2005 and published on December 1, 2005, is prior art to the ’392 patent under 35 U.S.C. §102(b) and (e) because it was published and filed, respectively, before the earliest claimed priority date, September 23, 2008. Modlin was applied by Examiner only to two dependent claims for its disclosure of a manifold sealably mounted to a chip with a gasket. (*See* Section VI.B.)

3. Chien et al., *Multiport flow-control system for lab-on-a-chip microfluidic devices*, Fresenius J Anal Chem (2001) 371 :106–111

Chien et al., *Multiport flow-control system for lab-on-a-chip microfluidic devices*, Fresenius J Anal Chem (2001) 371 :106–111 (“Chien,” Ex. 1007),

¹ Unless otherwise stated, all pin cites to page numbers correspond to the exhibit page numbering applied to the bottom of each exhibit (as opposed to the document’s intrinsic page numbering), whereas pin cites to paragraph or column/line numbers refer to the document’s intrinsic numbering.

published on July 27, 2001, is prior art to the '392 patent under 35 U.S.C. §102(b) because it was published more than one year before the earliest claimed priority date, September 23, 2008. Chien's publication information is attached as Ex. 1035, which is self-authenticating and subject to FRE 803(17) and 807.² Chien was not before the Examiner during prosecution.

4. Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain Reaction in Picoliter Droplets*, Anal. Chem. 2007, 79, 8471-8475

Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain Reaction in Picoliter Droplets*, Anal. Chem. 2007, 79, 8471-8475 ("Beer," Ex. 1034), published on July 27, 2001, is prior art to the '392 patent under 35 U.S.C. §102(b) because it was published more than one year before the earliest claimed priority date, September 23, 2008. Beer's publication information is attached as Ex. 1038. Beer was one of the four hundred eighty-three (483) references cited during *ex*

² Unless otherwise stated, all NPL publication information cited herein is self-authenticating and subject to FRE 803(6), 803(17) and 807. The publication information is also authenticated and shown to be made in the regular course of business (FRE 803(6)) and have circumstantial guarantees of trustworthiness (FRE 807) by the Davila Declaration (Ex. 1049.)

parte prosecution but that publication was not otherwise mentioned or discussed by the Examiner or the applicant.

5. U.S. Patent 6,176,962 to Soane et al.

U.S. Patent 6,176,962 to Soane et al. (“Soane,” Ex. 1028), issued on January 23, 2001 is prior art to the ’392 patent under 35 U.S.C. §102(b) because it was published more than one year prior to the earliest claimed priority date, September 23, 2008. Soane was not before the Examiner during prosecution.

6. U.S. Published Application 2008/0166720 to Hsieh et al.

U.S. Published Application 2008/0166720 to Hsieh et al. (“Hsieh,” Ex. 1018), filed on October 5, 2007, and published on July 10, 2008, is prior art to the ’392 patent under 35 U.S.C. §102(a) and (e) because it was published and filed, respectively, before the earliest claimed priority date, September 23, 2008. Hsieh was not before the Examiner during prosecution.

C. Relief Requested

Petitioner requests that the Board cancel claims 1-21 on the basis that they are unpatentable as obvious under pre-AIA 35 U.S.C. §103(a).

V. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (POSITA) at the time of the earliest claimed priority date (September 23, 2008) would have had a Ph.D. in chemical engineering, mechanical engineering, biomedical engineering, fluid dynamics, or a related discipline, with two years of work experience in the field of microfluidic devices. (Ex. 1003 ¶52.) Additional training or study would substitute for work experience and additional work experience or training would substitute for formal education. *Id.*

VI. OVERVIEW OF THE ‘392 PATENT

The ‘392 patent describes the alleged invention as comprising “a plate including an array of emulsion production units” and “a vacuum or pressure source . . . capable of driving a first fluid and a second fluid from respective first and second input wells of such unit and through the droplet generator, for collection as an emulsion in the output well of such unit.” (Ex. 1001 at 1:46-58.) Figures 4, 22, 23 and 24 (annotated with arrows below) are illustrative.

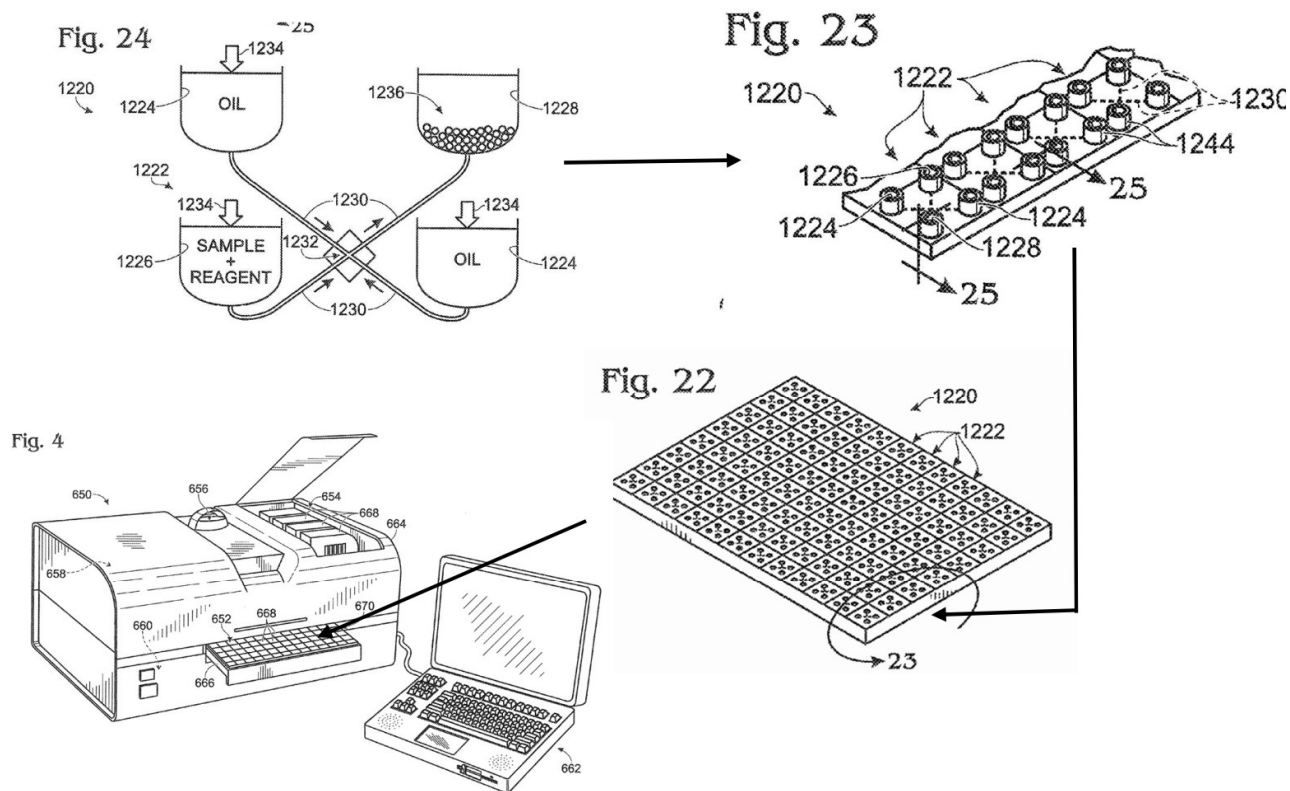


Fig. 4 shows that an instrument 650 receives plate 670 that includes reservoirs or wells 668 and a droplet generator. (*Id.* at 20:16-40.) Fig. 22 shows the plate and droplet generators. (*Id.* at 35:24-54.) Figure 23 is a close-up of area 23 of Fig. 22. (*Id.*) Figure 24 illustrates the four-port droplet generator 1222 of plate 1220. (*Id.* at 35: 41-55.)

In use, a pressure manifold is aligned with the wells 1224. Pressure 1234 is applied to fluid in the wells to drive the oil, sample and reagent through the channel intersection or junction 1232. (*Id.* at 35:27-55, see also Abstract, 1:46-58, 35:56-36:52.) At the junction 1232 droplets of the sample and reagent are formed in the oil, creating an emulsion which flows to output well 1228. (*Id.* at 35:27-55.)

A. Priority Date of the ‘392 Patent

The ‘392 patent claims priority to various provisional applications, the first of which was filed September 23, 2008. In the pending ITC proceeding, Patent Owner identified the priority date to which the claims of the related U.S. Patent 9,126,160 are entitled. Patent Owner alleged that the claims of the ‘160 patent, which correspond closely to those in the ‘392 patent, are entitled to the benefit of date of U.S. Provisional Application No. 61/271,538, filed July 21, 2009. (Ex. 1027 p. 2; Ex. 1050 at claims.)

Because each of the prior art references presented here is prior art even to the ‘392 patent’s earliest claimed priority date, Petitioner does not address whether the ‘392 patent is entitled to its claimed priority dates. Petitioner reserves the right to challenge the priority claims of the ‘392 patent.

B. Summary of the Prosecution History

During prosecution, the Examiner raised one art-based rejection against the independent claim. The single rejection was obviousness based only on Pollack et al. 2008/0038810. (Ex. 1002 pp. 253-54). The Examiner noted that Pollack discloses a droplet-based array multiplexed on a multi-well plate that includes the recited input wells and output wells. (*Id.*)

Pollack’s droplet generator is different than the T-junction and the cross-junction generators described above in the Technical Background. Instead, Pollack

teaches that “[d]roplets may be formed by energizing electrodes adjacent to the fluid reservoir causing a ‘finger’ of fluid to be extended from the reservoir. (Ex. 1020 ¶443.) In other words, droplets are formed by applying voltages to electrodes, not by using two pressure-driven fluid flows.

Applicant argued, and the Examiner ultimately agreed, that Pollack did not disclose the recited channel junction and vacuum/pressure source. (Ex. 1002 pp. 235-37, 214-16, 143-51). The Examiner allowed the claims on this basis. (*Id.* pp. 143-51.) The reasons for allowance states:

[T]he prior art fails to teach or fairly suggest a system for forming an array of emulsion that includes at least one input well, a second input well and an output well connected by a set of channels where the input wells form a channels junction with the output channel extending away from the junction. The prior art further fails to teach or fairly suggest the use of a vacuum or pressure source to create a pressure differential between the input and output wells in order to drive the continuous and dispersed phases where these limitations are in combination with the claim as a whole.

(*Id.* p. 150.)

VII. CLAIM CONSTRUCTION

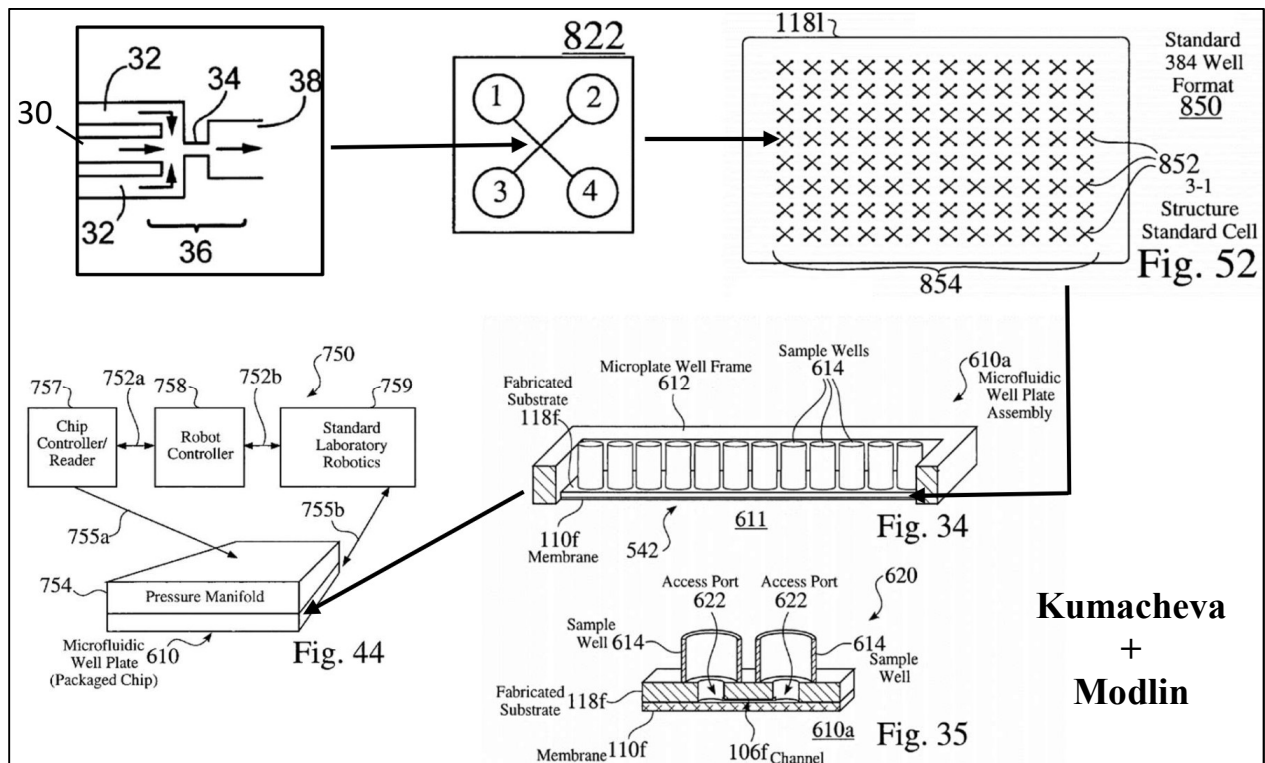
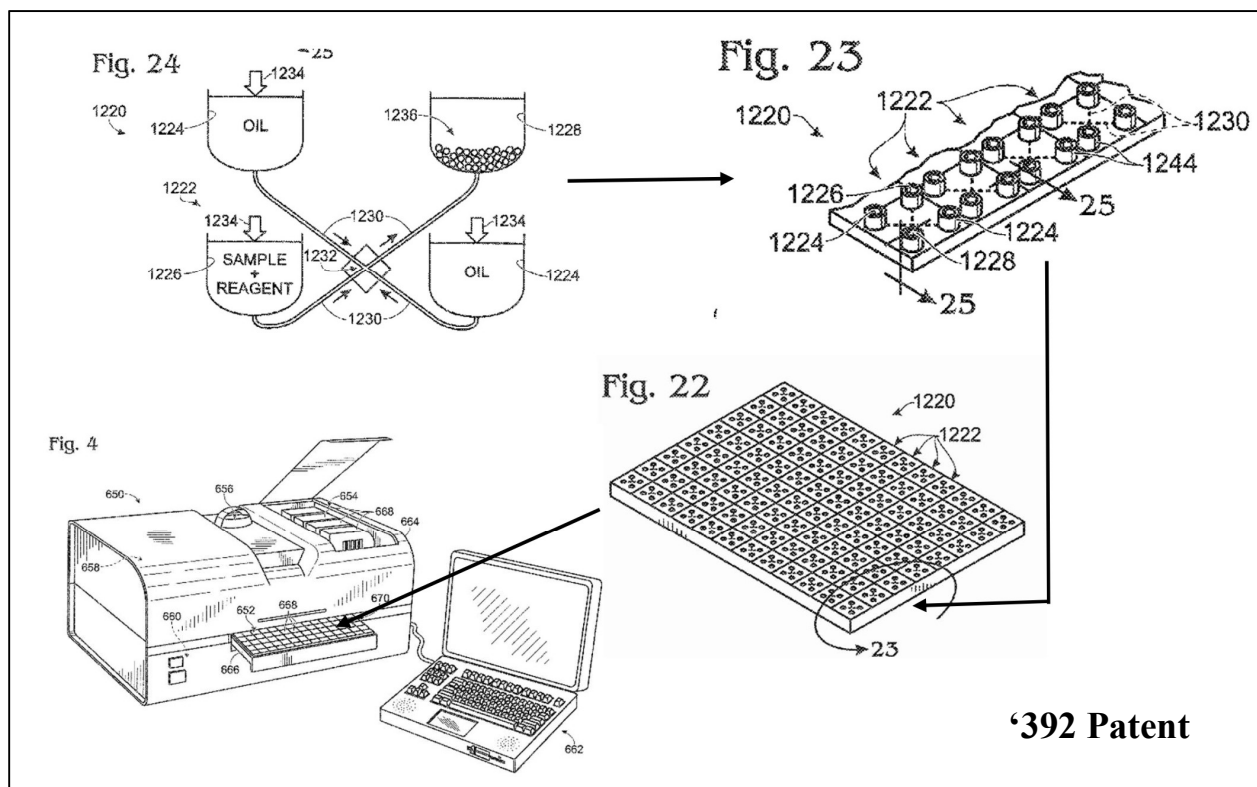
In an *inter partes* review, the terms in the challenged claims are to be given their plain meaning consistent with the specification under the broadest reasonable interpretation standard. *Cuozzo Speed Technologies, LLC v. Lee*, 136 S. Ct. 2131, 2139, 2141 (2016); *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir. 2003). Unless otherwise stated Petitioner adopts that standard for all of the terms set forth in the claims of the ‘392 patent. Petitioner reserves the right to contest any claim construction proffered by Patent Owner in this proceeding.

VIII. GROUNDS FOR FINDING THE CHALLENGED CLAIMS INVALID

Pursuant to Rule 42.104(b)(4)-(5), the grounds for finding the challenged claims invalid are identified below and discussed in the Gandhi Declaration. (Ex. 1003.)

A. Ground 1: Claims 1, 3-4, 6, 8-17 and 19-21 Are Rendered Obvious by Kumacheva in View of Modlin

Claims 1, 3-4, 6, 8-17 and 19-21 are rendered obvious by Kumacheva in view of Modlin. Kumacheva was not before the Examiner. Modlin was cited by the Examiner but applied only against two dependent claims (claims 3-4), and only relied upon for its disclosure of a manifold and gasket limitation. (Ex. 1002 p. 257.) As depicted below, the preferred embodiment of the '392 patent corresponds closely to the combined system of Kumacheva and Modlin.



1. Independent Claim 1

Kumacheva and Modlin render independent claim 1 of the '392 patent obvious. (Ex. 1003 ¶53.)

Kumacheva teaches an array of emulsion production units. Kumacheva “provides devices for the parallelization of the formation of droplets in a multiple droplet generator integrating two or more parallel flow-focusing devices (FFDs).” (Ex. 1004 at Abstract; Ex. 1017 p. 39.) The Kumacheva multiple droplet generator is shown in Fig. 4 (right), depicting a sheet 14 having a relief pattern of four microfluidic flow-focusing devices (FFDs) 20. (Ex. 1004 ¶¶61-65; Ex. 1017 p. 16-18.) In each FFD 20 (shown individually in the expanded view from Fig. 2, right), “[t]wo immiscible liquids, a droplet phase A, and a continuous phase B, are supplied to the central channel 30 and side channels 32 of the FFD, respectively. The liquids are forced through a narrow orifice 34 in which a thread of liquid A breaks up and releases droplets 62.” (Ex. 1004 ¶61; Ex. 1017 p. 16.) This type of FFD or cross-junction droplet generator was well known as of June 2008. (Ex. 1015 ¶¶59-66; Ex. 1016 pp. 2-3; Ex. 1018 ¶¶21-27; Ex. 1013; Ex. 1003 ¶54).

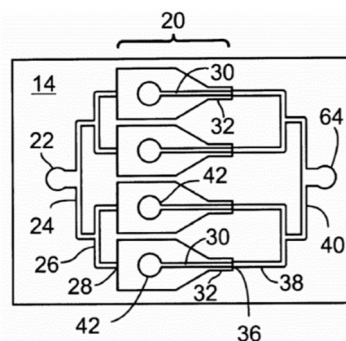
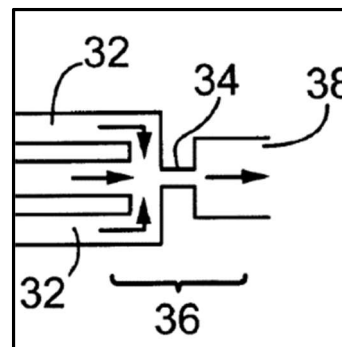
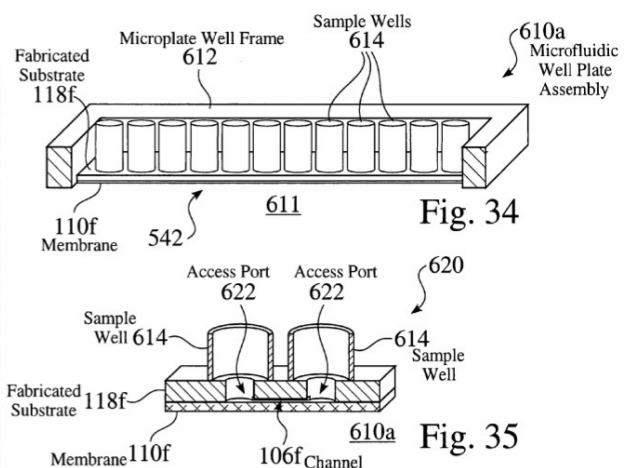
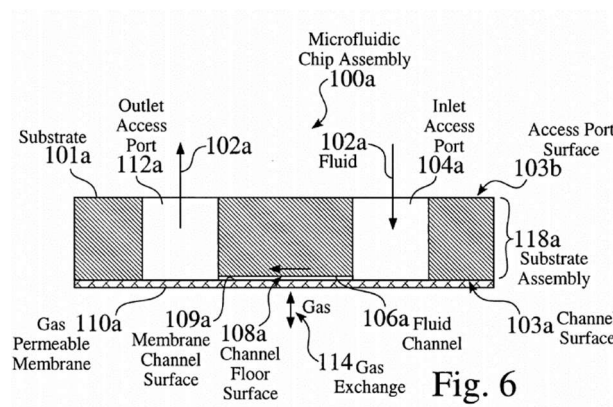


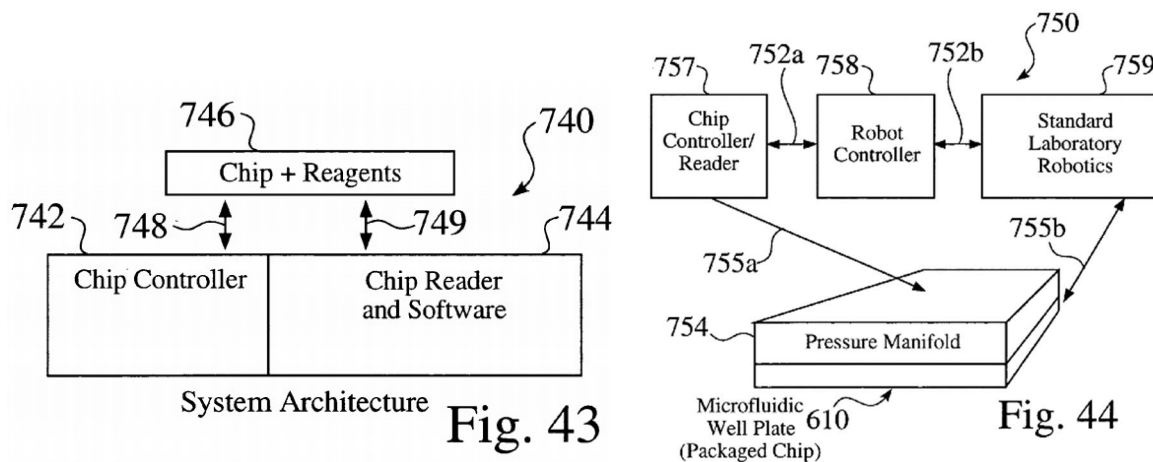
FIG. 4



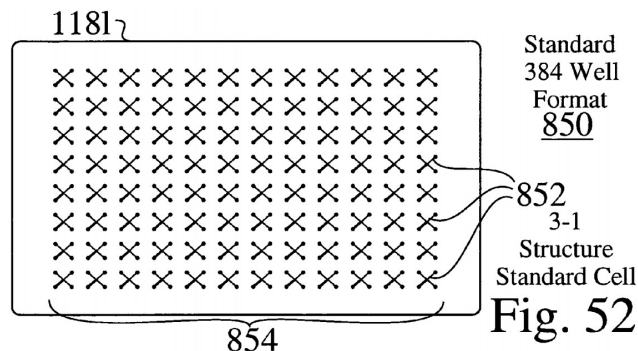
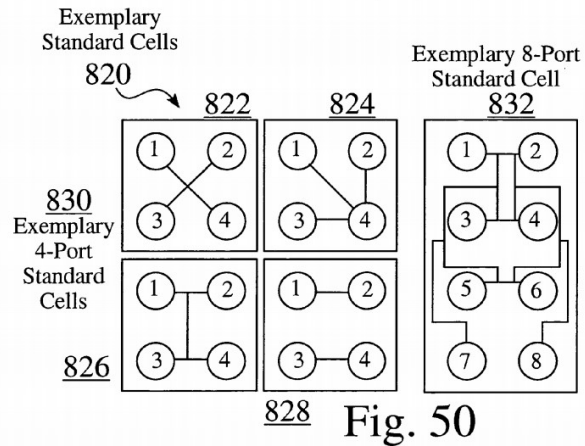
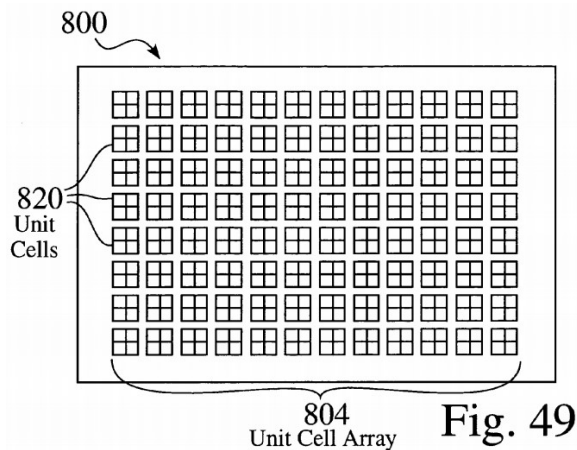
Modlin teaches a microplate well configuration for parallelizing multiple microfluidic circuits. Modlin discloses a microfluidic system with two basic components: i) a **well plate assembly 610** consisting of a microfluidic chip having fluid channels, access ports, and a well frame having wells aligned with the access ports, and ii) an **instrument 740/750** to drive the fluids from input wells, through the fluid channels, to output wells. (Ex. 1005 ¶¶114, 176-180; Ex. 1003 ¶55.) The microfluidic chip 100 is depicted in Fig. 6 of Modlin and includes a substrate 118, a membrane 110, and fluid channels 106 extending between access ports 102, 104 that span the substrate 118. (Ex. 1005 ¶114). The chip 100 (comprising substrate 118 and membrane 110) is coupled to a microplate well frame 612 that includes sample wells 614 aligned with the access ports 102/104/622 of the substrate 118. The resulting assembly is a **microfluidic well plate assembly 610**. (*Id.* ¶¶176-180; Ex. 1003 ¶55.)



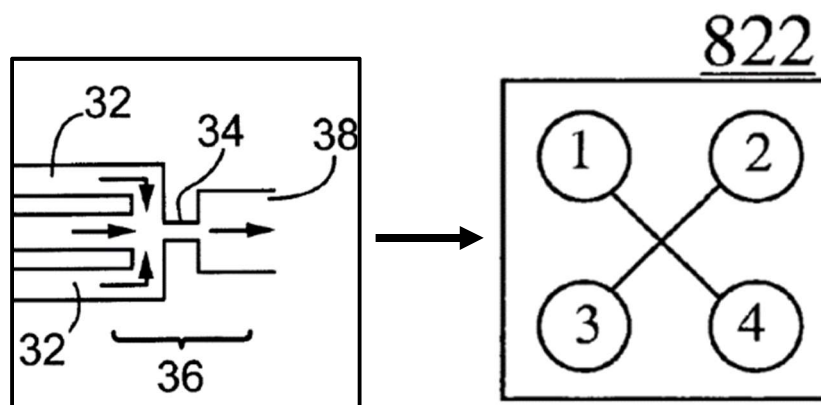
The **instrument 740/750** includes a “system 740 for operating a microfluidic chip and associated reagents 746 comprising a chip controller 742 and a chip reader and associated software 744.” (Ex. 1005 ¶192-202.) In a constant pressure control regime, an “externally controlled source would preferably provide a source of constant pressure to the inlet or outlet wells and thus control flow in the channels.” (*Id.* ¶193.) This pneumatic or hydraulic pressure is provided by pressure manifold 754, which is sealed against the microfluidic well plate assembly 610. (*Id.* ¶201-02.) The chip controller 742 includes an “accurately regulated source of gas” to “provide controlled flow velocities in the range of 0 to 1 meter per second with a precision of . . . better than 1 micron per second.” (*Id.* ¶195.)



The well plate assembly 610 may be “packaged in an industry standard microplate format . . . designed to be compatible with industry standard physical conventions [which] provides an interface 755b to standard laboratory robotics.” (*Id.* ¶201 (emphasis added).) Fig. 49 illustrates a layout having an “industry standard 384 well format, each unit cell having up to 4 access ports” as shown in Fig. 50. (*Id.* ¶208-10.) When unit cell 822 is used, the resulting substrate 118 has the configuration shown in Fig. 52. (*Id.* ¶213.) Using this type of format provides “well to well spacing or well pitch . . . to enable microfluidic well plates according to aspects of the present invention to be compatible with standardized fluid handling equipment.” (*Id.* ¶211.)

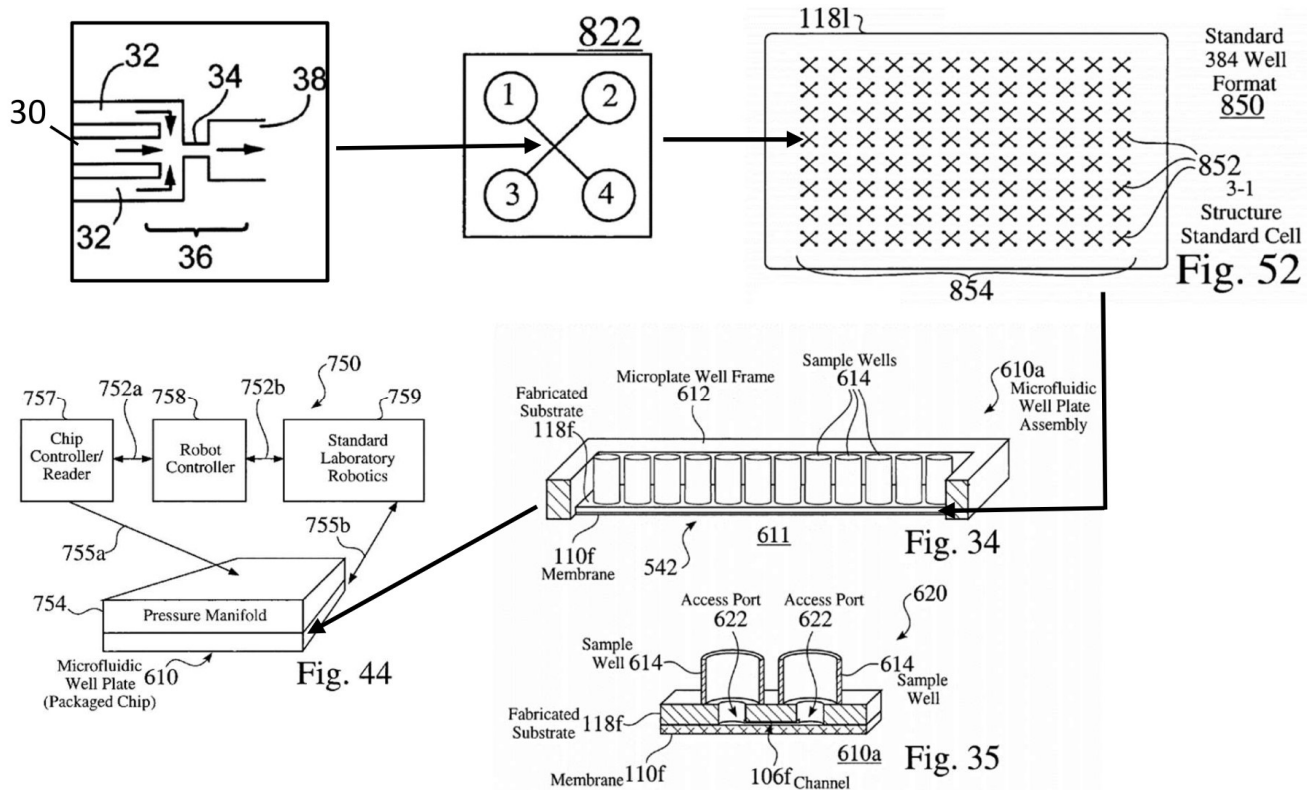


A skilled artisan would have considered it obvious to modify the parallel flow-focusing droplet generators of Kumacheva according to the industry standard well plate configuration of Modlin. (Ex. 1003 ¶58.) For example, a skilled artisan would have considered it obvious to configure Kumacheva’s FFD 36 in Modlin’s “3-1 combiner” unit cell 822. (*Id.*) Access ports 1 and 4 are connected to the channels 32 of Kumacheva’s flow-focusing device (FFD) and these carry the continuous phase. (Ex. 1003 ¶59.) Port 3 is connected to channel 30 and this carries the aqueous (dispersion) phase. (*Id.*) Droplets are generated at the cross-shaped junction and routed through the output channel 38 to output port 2. (*Id.*)



In the resulting well plate assembly 610 of the Combined System

(illustrated below), the substrate 118 includes 96 unit cells 822, each of which has four wells 614 connected to an FFD 36. (*Id.*) The continuous phase is provided in the wells 614 above ports 1 and 4 and the dispersion phase is provided in the well 614 above port 3. (*Id.*) The emulsion generated at the channel junction is collected in the well 614 above port 2. (*Id.*) The well plate assembly 610 is sealably mated with Modlin's pressure manifold 754 which provides pneumatic (air) pressure to drive the fluids among the wells for each unit cell 822. (*Id.*)



Given a well pitch of 4.5 mm for a 384 well plate, a well diameter and height of 2.25 mm, a droplet diameter of around 30 μm , and a 3:1 ratio of continuous phase to dispersion phase, the **output well of each unit cell would be configured to hold over 125,000 droplets.** (*Id.* ¶60) At the time of filing, emulsion or droplet based PCR typically involved analysis of less than 5,000 droplets. (*Id.*) Each unit cell of the Combined System would thus hold **25X more droplets than needed for microfluidic PCR.** (*Id.*) On a 96 well plate (providing 24 unit cells), the larger output wells (around 4.5 mm) would each hold about 1,250,000 droplets, about **250X more than needed for microfluidic PCR.** (*Id.*) The suitability of the Combined System for PCR is discussed further in Ground 4, which discussion is incorporated herein by reference.

A skilled artisan would have been motivated to combine Kumacheva with Modlin in this manner. First, Kumacheva expressly suggests that the fluids may be routed to and from the emulsion generator units in various ways, for instance through additional manifolds. (Ex. 1004 ¶68; Ex. 1017 pp. 13, 16-18.) Kumacheva teaches that such modifications “may be useful in some embodiments where mixing, concentration, dilution, or **change in composition of droplet phase**

or continuous phases is needed.” (*Id.* (emphasis added).³) Incorporating Modlin’s teachings of connecting each fluidic circuit to its own input and output wells in a unit cell would permit use of a wide variety of different droplet phases and continuous phases on the same plate simultaneously, increasing efficiency of running large numbers of droplet generation operations. (Ex. 1003 ¶61.)

Second, Kumacheva expressly suggests using the device to perform biological and biochemical analyses by noting that “[m]ultichannel microfluidic devices have been used for DNA separation, parallel PCR assays, detection of enzymatically-generated fluorescence and linear temperature gradients, capillary electrophoresis for immunoassays, and chiral separation.” (Ex. 1004 ¶14; Ex. 1017 pp. 9-10.) Configuring the Kumacheva droplet generators in a unit cell arrangement on a microwell plate assembly as disclosed by Modlin would enable the droplet generators to perform assays on different emulsions in parallel as taught by Modlin. (Ex. 1003 ¶62.) Providing each droplet generator in a separate unit cell permits different biochemical, biological, or chemical assays to be performed on samples from multiple different patients on a single chip. (*Id.*) Alternatively, the unit cells could be used to prepare different emulsions at the same time, *e.g.*,

³ Hereafter, all emphasis is added unless otherwise indicated.

emulsions having different dispersion or continuous phases, greatly enhancing the utility of the Kumacheva droplet generator. (*Id.*)

Third, configuring the Kumacheva droplet generators in a unit cell arrangement on a microwell plate assembly as disclosed by Modlin would substantially increase compatibility with industry standard laboratory equipment and reduce cost. Modlin expressly teaches that “one aspect of the present teachings is to intentionally provide compatibility with laboratory robotic standards enabling products made according to the present teachings to be readily used in conjunction with industry standard fluid dispensing, detection, and other robotics and automated processing equipment.” (Ex. 1005 ¶¶201, see also ¶¶172, 176-177, 202, 204.) Modlin teaches that such platforms provide low cost and standardized methods to enable the performance of 96, 384, 1536, or 3456 assays in parallel. (Ex. 1005 ¶¶105, 312.), reducing the cost per assay. (Ex. 1005 ¶¶238-240; Ex. 1003 ¶63.) A skilled artisan would readily appreciate that configuring Kumacheva’s droplet generators according to Modlin’s microwell plate would generate these same benefits. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-421 (2007) (holding that obviousness may be demonstrated by use of known technique to improve similar devices in the same way) (Ex. 1003 ¶63.)

Fourth, laying out the Kumacheva droplet generators in a plate assembly as disclosed by Modlin would substantially increase the degree of parallelization from

four (as disclosed in Kumacheva) to 24, 96 or more. (Ex. 1005 ¶¶105, 209, 312.) Increased parallelization was widely known and widely practiced as of September 2008, and the associated benefits were apparent. (Ex. 1003 ¶64.) As noted by Kawai, Karnik and Nisisako, for example, use of parallel emulsion generators substantially increases throughput and makes the devices useful in the context of industrial scale synthesis. (Ex. 1037 pp. 1-3; Ex. 1021 ¶239; Ex. 1031 pp. 1-7; Ex. 1024; Ex. 1030; Ex. 1003 ¶64.) A skilled artisan would readily have understood that incorporating the Kumacheva droplet generator into the Modlin plate assembly would have substantially increased its degree of parallelization, and thus throughput. (Ex. 1003 ¶64.) In other words, the Modlin plate assembly would be used to improve upon similar devices (Kumacheva) in the same way to provide the same function (providing increased throughput). *KSR*, 550 U.S. at 417 *Id.*

A skilled artisan would have had a reasonable expectation of success in making the Combined System. (Ex. 1003 ¶65.) Modlin explains “[m]anufacturing of the assemblies of the present teachings may be carried out by any number of microfabrication techniques that are well known in the art.” (Ex. 1005 ¶160.) Modlin explicitly teaches that the plate assemblies may be fabricated by techniques including lithographic techniques, laser drilling, micromilling, injection molding, embossing or stamping. (*Id.* ¶¶160-74.) **Modlin in fact provides significantly more teaching on fabrication of the plate assemblies than the ‘392 patent,**

which merely states that “the upper and lower sections [of the plate] . . . sections may be manufactured by any suitable method, such as by injection molding a thermoplastic material.” (Ex. 1001 at 60:25-30.) Thus, the Combined System could have been readily fabricated according to the methods disclosed by Modlin and Kumacheva, particularly in view of the level of skill in the art which is implicitly acknowledged by the ‘392 patent’s failure to describe any manufacturing techniques. (Ex. 1003 ¶¶65.)

Accordingly, a skilled artisan would have 1) considered it obvious to modify the parallel flow-focusing droplet generators of Kumacheva according to the microplate well configuration of Modlin to arrive at the Combined System and 2) had a reasonable expectation that the Combined System would have successfully resulted in a microfluidic droplet system such as that claimed in the ‘392 patent without undue experimentation. (Ex. 1003 ¶¶58-66.)

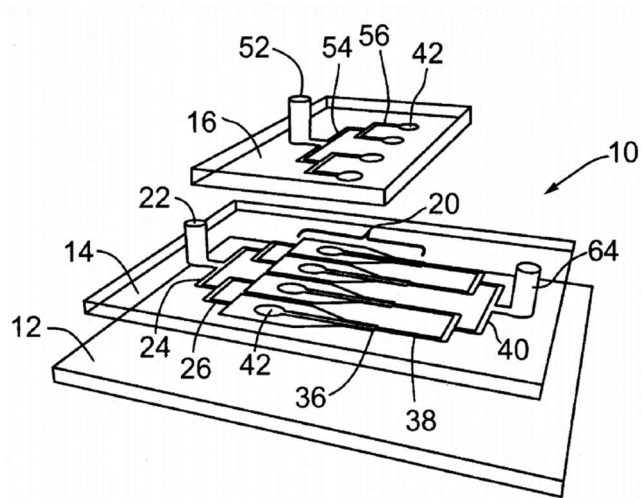
Preamble

The preamble of claim 1 recites “[a] system for forming an array of emulsions, comprising.”

Assuming arguendo that the preamble is limiting, Kumacheva discloses a system for forming an array of emulsions. (Ex. 1003 ¶67.) Kumacheva discloses that her “invention provides devices for the parallelization of the formation of droplets in a multiple droplet generator integrating two or more parallel flow-focusing devices (FFDs) with either identical, or different, geometries.” (Ex. 1004 at Abstract; Ex. 1017 p. 39.) “In the parallel identical FFDs, emulsification generates droplets with a narrow (below 4%) polydispersity despite weak coupling between the identical flow-focusing devices.” (*Id.*, see also Ex. 1004 ¶¶22-38, 61-66; Ex. 1017 pp. 11-13, 16-18.)

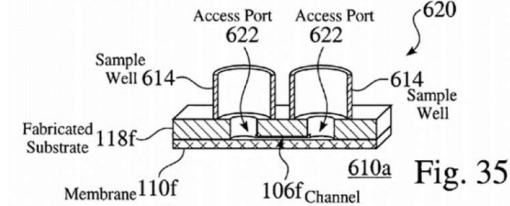
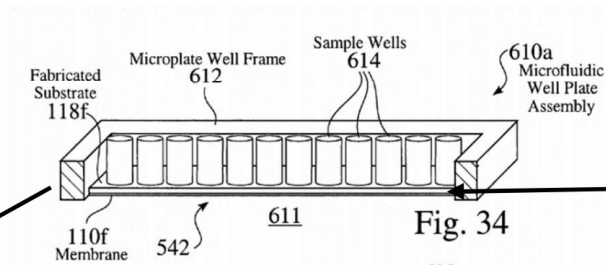
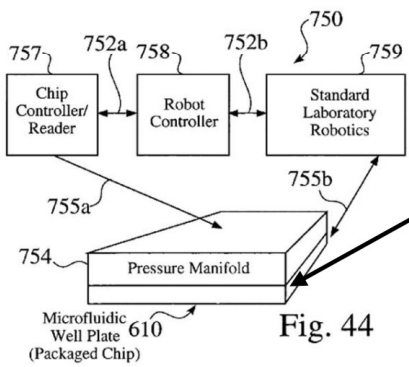
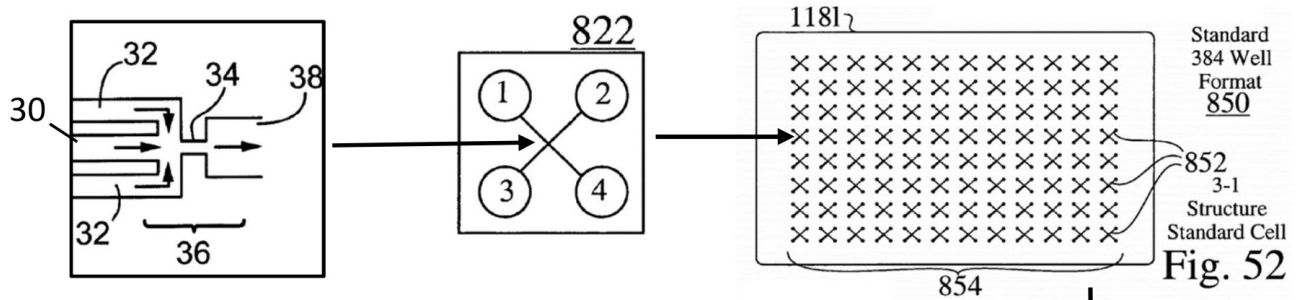
Kumacheva system is thus configured to

produce an “array of emulsions,” meeting the language of the preamble. (Ex. 1003 ¶67.)



The Combined System also produces an array of emulsions. (Ex. 1003

¶¶68-69.) In the non-limiting example depicted below, the Kumacheva droplet generators 36 in each unit cell 822 generate a separate emulsion. (Id.)



Element 1[a]

Claim element 1[a] recites “a plate including an array of emulsion production units.”

Kumacheva’s patterned sheet 14 meets element 1[a] and, in the Combined System, microfluidic well plate assembly 610 meets element 1[a]. (Ex. 1003 ¶¶70-75.)

Kumacheva discloses a quadra-droplet generator 10 having four parallel droplet or emulsion generators 20. (Ex.

1004 Abstract, ¶¶61-65; Ex. 1017 pp. 16-

18.) “The intermediate and the top

components of the device (**sheets 14** and 16,

respectively) are patterned, as shown in

FIGS. 4 and 5. Particularly, **sheet 14** has a

relief pattern of **four (4)** (but it may be a

plurality) microfluidic flow-focusing devices 20” (Ex. 1004 ¶¶61-65; Ex.

1017 at 16-18.) Kumacheva’s patterned sheet 14 thus meets claim 1[a]. (Ex. 1003

¶71.)

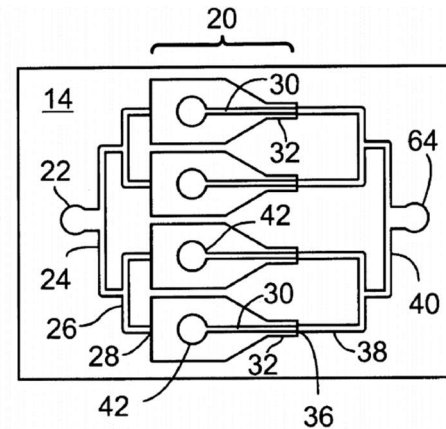
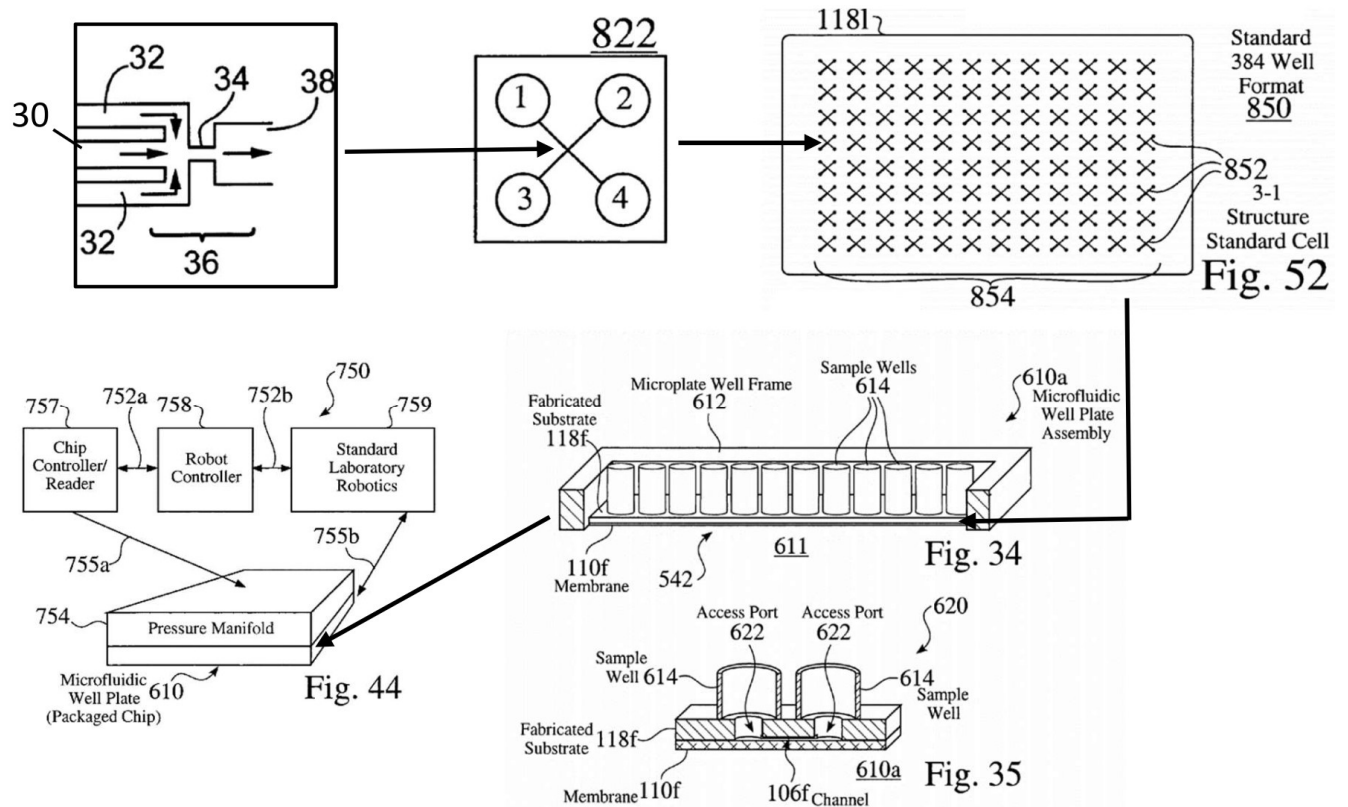


FIG. 4

In the Combined System Modlin’s microfluidic well plate assembly 610 meets element 1[a]. As discussed above, it would have been obvious to configure the parallel emulsion generator units of Kumacheva according to the microfluidic well plate format taught by Modlin. (Ex. 1003 ¶72.) In the non-limiting example

depicted below, the microfluidic well plate assembly 610 meets element 1[a]. (Ex. 1004 ¶¶62; Ex. 1017 pp.16-19; Ex. 1005 ¶¶177-178, 201-202, 208-214; Ex. 1003 ¶¶72, 75.)



Element 1[a][i]

Claim element 1[a][i] recites “each unit including at least one first input well to hold a continuous phase for an emulsion.” The ’392 explains that “any of the emulsions disclosed herein may be a water-in-oil (W/O) emulsion (*i.e.*, aqueous droplets in a continuous oil phase).” (Ex. 1001 at 10:51-53.)

In the Combined System, the wells above ports 1,4 of each unit cell meet element 1[a][i]. (Ex. 1003 ¶80.)

Kumacheva teaches that “[t]wo immiscible liquids, a droplet phase A, and a **continuous phase B**, are supplied to the central channel 30 and side channels 32 of the flow-focusing device (FFD),

respectively.” (Ex. 1004 ¶61; Ex. 1017 at 16; see also Ex. 1004 ¶¶31, 37, 70, Ex. 1017 pp. 13, 19, 31; Ex. 1003 ¶78.) “A 2 wt % solution of a nonionic surfactant Span 80 in a light mineral oil was used as a **continuous**

phase (introduced as liquid B).” (Ex. 1004 ¶70; Ex. 1017 p. 19.)

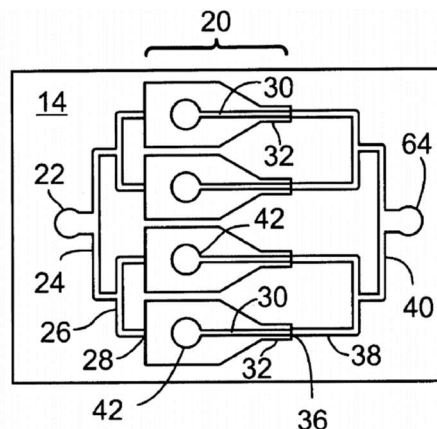
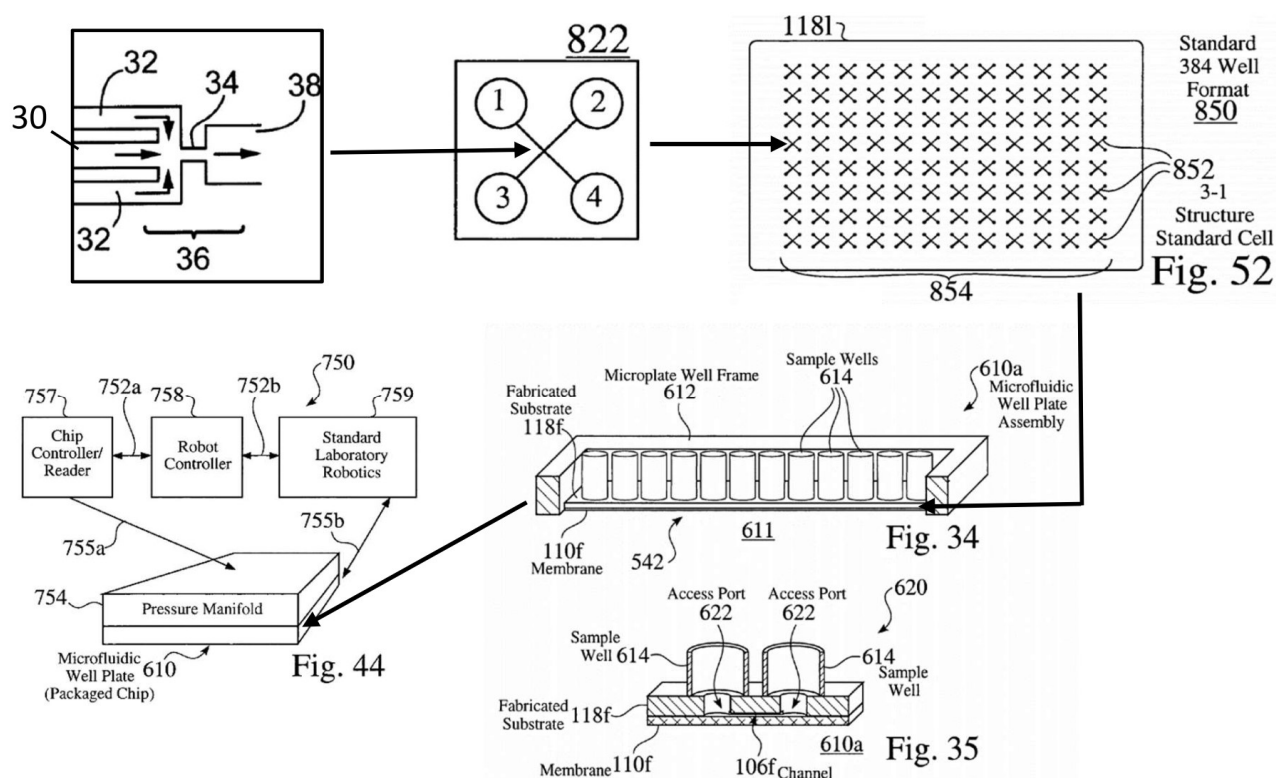


FIG. 4

Modlin teaches that the various unit cells include upwardly extending sample wells 614 as depicted in Fig. 35. (Ex. 1005 ¶¶175-180; Ex. 1003 ¶79.)

In the Combined System, Kumacheva's continuous phase B is provided, for example, in wells 614 above ports 1 and 4, each of which are connected to the droplet generator junction 36 by channels 32. (Ex. 1003 ¶80.)



The wells 614 above ports 1, 4 meet element 1[a][i] in the combined system, an example of which is depicted above. (*Id.* ¶¶80-81.)

Element 1[a][ii]

Claim element 1[a][ii] recites that each emulsion production unit include “a second input well to hold a dispersed phase for an emulsion.” The “dispersed phase” is an aqueous phase in the preferred embodiment. (Ex. 1001 at 10:15-19.)

In the Combined System, the well above port 3 in each unit cell meets element 1[a][ii]. (Ex. 1003 ¶83.)

Kumacheva teaches that “[t]wo immiscible liquids, a **droplet phase A**, and a continuous phase B, are supplied to the central channel 30 and side channels 32 of the flow-focusing device (FFD), respectively.” (Ex. 1004 ¶61; Ex. 1017 at 16; see also Ex. 1004 ¶¶31, 37, 70, Ex. 1017 pp. 13, 18, 31; Ex. 1003 ¶82.) “Filtered, **deionized water was used as a droplet phase (introduced as liquid A).**” (Ex. 1004 ¶70; Ex. 1017 p. 19.)

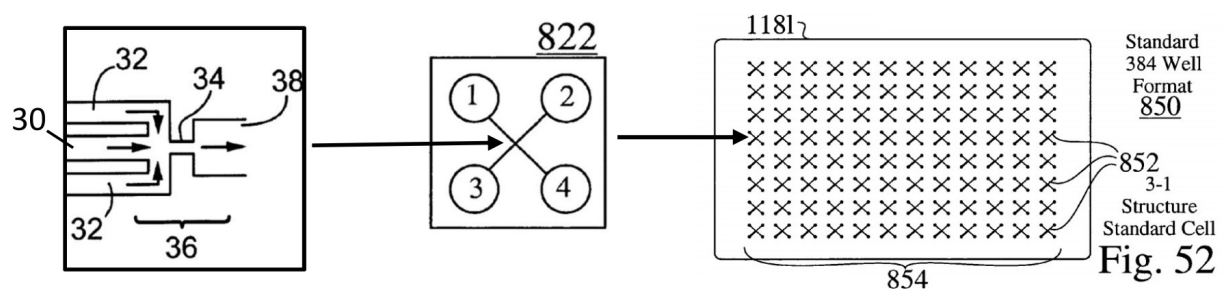
In the Combined System, *e.g.*, as depicted above, Kumacheva’s aqueous droplet phase A is provided in the well 614 above port 3, which is connected to the droplet generator junction 36 by channel 30. (Ex. 1003 ¶83.)

The dispersion phase well of the Combined System meets element 1[a][ii]. (Ex. 1003 ¶84.)

Element 1[a][iii]

Claim 1[a][iii] recites “an output well connected to the first and second input wells by a set of channels that form a channel junction, the set of channels including at least two input channels extending separately from the input wells to the channel junction and an output channel extending from the channel junction to the output well.”

The flow focusing device 36 of the Combined System is the recited “channel junction.” (Ex. 1003 ¶85.) As taught in Kumacheva “[t]wo immiscible liquids, a droplet phase A, and a continuous phase B, are supplied to the central channel 30 and side channels 32 of the flow-focusing device (FFD), respectively.” (Ex. 1004 ¶61; Ex. 1017 at 16; see also Ex. 1004 ¶¶31, 37, 70, Ex. 1017 pp. 13, 19, 31; Ex. 1003 ¶85.) In the Combined System the FFD 36 is the recited channel junction. (Ex. 1003 ¶85.)



The Combined System includes input channels that extend from the respective input wells. (Ex. 1003 ¶85.) In the example of Combined System illustrated above, channels 30, 32 extend from the input wells 1, 4 for the

continuous phase to the channel junction (FFD). *Id.* Channel 30 extends from the input well 3 for the aqueous dispersion phase to the channel junction (FFD). *Id.*

The Combined System includes “an output channel extending from the channel junction to the output well.” (*Id.*) Kumacheva teaches that “Liquid A . . . travels downstream via the central microchannel 30 through orifice 34 to the outlet microchannels 38.” (Ex. 1004 ¶62; see also Ex. 1017 pp. 13, 16-18.) “Liquid B . . . travels through microchannel 32 through orifice 34 to the outlet microchannels 38.” (*Id.*) In the example of the Combined System illustrated above, channel 38 extends from the channel junction (FFD) to the from the output wells 2 for the water-in-oil emulsion. (*Id.*)

The output well of the Combined System thus meets element 1[a][iii]. (Ex. 1003 ¶¶85-86.)

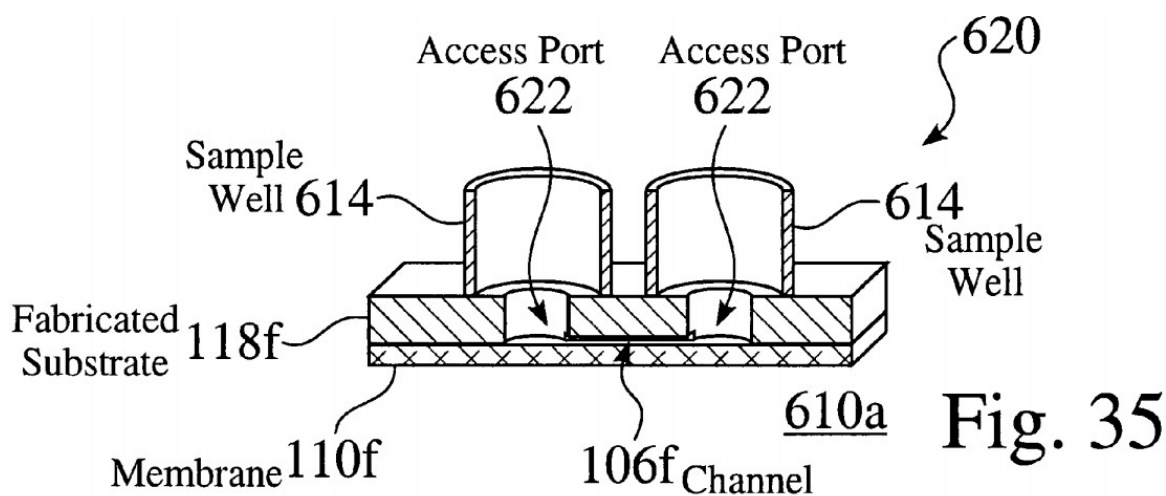
Element 1[a][iv]

Claim 1[a][iv] recites “each channel of the set of channels being circumferentially bounded.”

Kumacheva teaches that the channels are circumferentially bounded. (Ex. 1003 ¶87.) It discloses that channels are formed in the bottom of plates 14 and 16. (Ex. 1004 ¶¶64-67; Ex. 1017 pp. 16-19; Ex. 1003 ¶87.)) The plate 16 is sealed to plate 14, thereby forming the bottom wall of the channels 54/56 and well 52. (*Id.*) In a similar fashion plate 14 is sealed to plate 16, thereby forming the bottom wall

of channels 36/38 and wells 22/64. (*Id.*) Kumacheva's channels are thus circumferentially bounded, meeting element 1[a][iv]. (Ex. 1003 ¶187.)

The channels of the Combined System are circumferentially bounded. (Ex. 1003 ¶¶88-90.) In the illustrative example of the combined system illustrated above, the channel network connecting wells 1-4 is circumferentially bounded as shown in the cutaway view of Modlin's Fig. 35, reproduced below. (*Id.*) The Combined System thus meets element 1[a][iv]. (*Id.*)



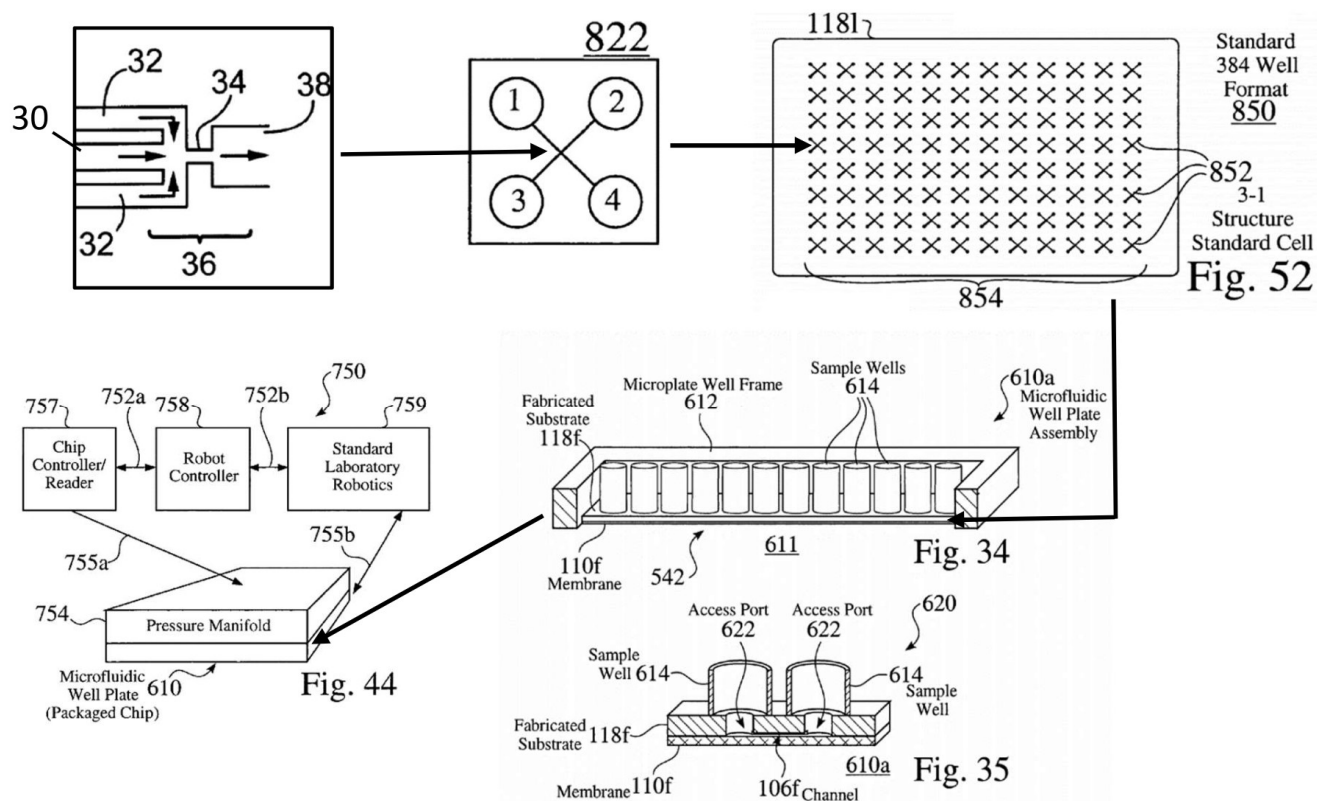
Moreover, Kumacheva and Modlin render element 1[a][iv] obvious because they teach that fluids may be driven through the fluidic circuit with positive pressure. (Ex. 1004 ¶84; Ex. 1017 p. 19; Ex. 1005 ¶187.) In order to use positive pressure to drive the fluids, the channels must be sealed (i.e., circumferentially bounded) and not open on any side. (Ex. 1003 ¶¶89-90.)

Element 1[b]

Claim 1[b] recites “a vacuum or pressure source configured to be connected operatively to wells of the plate to form a pressure drop between the input wells and the output well of each unit to drive the continuous phase and the dispersed phase from the first and second input wells of the unit to the channel junction, at which droplets of the dispersed phase are generated, and through the output channel for collection in the output well of the unit.”

Kumacheva discloses the recited vacuum or pressure source for forming a pressure drop between input and output wells to drive fluid flow in microfluidic channels as recited in element 1[b]. (Ex. 1003 ¶92.) Kumacheva discloses that fluids are supplied with pumps to the inlets 42, 42b, 42c, thus creating a pressure drop between the inlets and the outlet. (Ex. 1004 ¶¶64-70, 84; Ex. 1017 pp. 16-19; Ex. 1003 ¶92.)) “Liquids A and B were supplied to the quadra-droplet generator 10 (QDG) using two separate syringe pumps (PHD 2000, Harvard Apparatus, MA).” (Ex. 1004 ¶70; Ex. 1017 p. 19.) “Liquid A enters via opening 42 and travels downstream via the central microchannel 30 through orifice 34 to the outlet microchannels 38. Liquid B enters via side microchannels 26 and travels through microchannel 32 through orifice 34 to the outlet microchannels 38.” (Ex. 1004 ¶62; Ex. 1017 pp. 16-19.) As the fluids pass through the channels and junction, the pressure drops by virtue of the resistance to flow created by the channels and the

constriction. (Ex. 1033; Ex. 1007 pp. 2-3; Ex. 1003 ¶92.) Kumacheva’s pumps thus meet the recited “pressure or vacuum source.”



The Combined System also includes the recited vacuum or pressure source for forming a pressure drop between input and output wells to drive fluid flow in microfluidic channels as recited in element 1[b]. (Ex. 1003 ¶94.) Modlin’s instrument 740/750 includes a “system 740 for operating a microfluidic chip and associated reagents 746 comprising a chip controller 742 and a chip reader and associated software 744.” (Ex. 1005 ¶¶192-202.) In a constant pressure control regime, an “externally controlled source would preferably provide a source of

constant pressure to the inlet or outlet wells and thus control flow in the channels.” (*Id.* ¶193.) This pneumatic or hydraulic pressure is provided by pressure manifold 754, which is sealed against a microfluidic well plate assembly 610. (*Id.* ¶¶201-02.) The chip controller 742 includes an “accurately regulated source of gas” to “provide controlled flow velocities in the range of 0 to 1 meter per second with a precision of . . . better than 1 micron per second.” (*Id.* ¶195.)

In the exemplary combined system depicted above, pressure is applied at input wells 614 above access ports 1, 3 and 4, to drive the emulsion to the output well above port 2. (Ex. 1003 ¶94.) As noted above, as the fluids pass through the channels and junction, the pressure drops by virtue of the resistance to flow created by the channels and the constriction. (Ex. 1033; Ex. 1007 pp. 2-3; Ex. 1003 ¶94.)

The Combined System thus meets element 1[b]. (Ex. 1005 ¶¶186-190, 219-225; Ex. 1003 ¶95.)

Accordingly, claim 1 is rendered obvious by Kumacheva taken in view of Modlin.

2. Dependent Claims 3-4

Claims 3-4 depend from claim 1, and the analysis for claim 1 in Section

VIII.A.1 is incorporated by reference.⁴ Claim 3 recites that “an instrument including the vacuum or pressure source and a manifold, wherein the vacuum or pressure source is configured to be connected operatively to wells of the plate via the manifold.” Claim 4 recites “one or more gaskets that engage the plate and the manifold to form a seal between the manifold and the wells of the plate to which the vacuum or pressure source is configured to be connected operatively.”

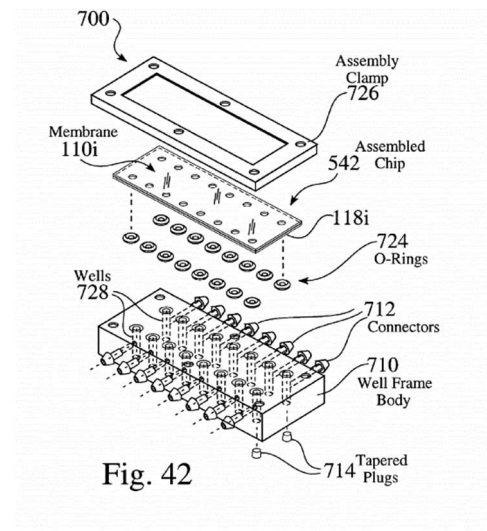
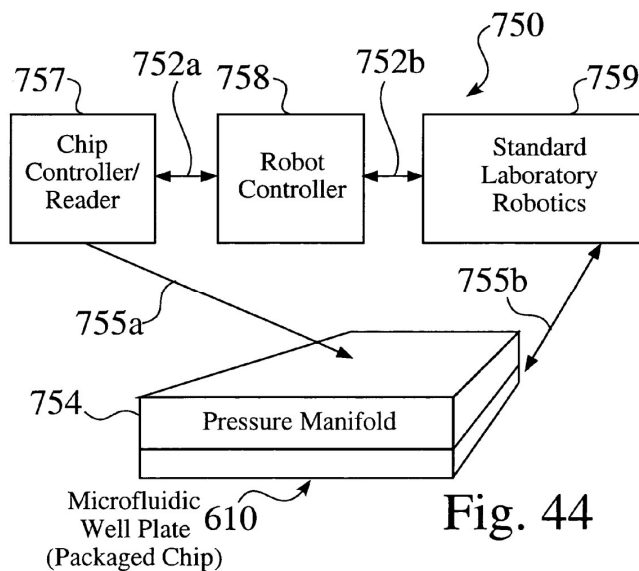
Modlin teaches a manifold configured to operatively connect to wells and seal against the wells via a gasket as recited in claims 3-4. (Ex. 1003 ¶¶96-99.)

With reference to Fig. 44, reproduced below, Modlin teaches that

“[c]ommunication between chip controller and reader 757 and **pressure manifold 754** takes place via interface 755a. Manifold 775 [sic 754] is **mechanically aligned and sealably mounted to packaged chip 610** and distributes the pneumatic, hydraulic, electronic, mechanical, or optical signals to and from the chip controller and reader 757 to their intended destinations on packaged chip 610.” (Ex. 1005 ¶¶201-02.) In one embodiment, a manifold-to-chip seal is provided by **o-rings 724** and in another “**compressible gasket materials.**” (Ex.

⁴ Hereafter, the analysis for the base claim(s) of any dependent claim is incorporated by reference into the analysis for the dependent claim.

1005 ¶¶153, 186-190; Ex. 1003 ¶97.) A **gasket** is “a material (such as rubber) or a part (such as an O-ring) used to make a joint fluid-tight.” (Ex. 1036.) Modlin’s pressure manifold 754 and well frame body 710 constitute the recited “manifold” and the o-rings or “compressible gasket materials” constitute the recited “gasket.” (Ex. 1003 ¶97.)



The Combined System described in connection with claim 1 also includes a manifold configured to operatively connect to wells and seal against the wells via a gasket. (Ex. 1003 ¶99.) As noted above, in the Combined System the microfluidic well plate is placed into “industry standard fluid dispensing, detection and other robotics and automated processing equipment” to drive the fluids among the microwells to “perform[] chemical reactions and/or biochemical, biological, or chemical assays analyses” as taught by Modlin. (Ex. 1005 ¶¶15, 201; Ex. 1003 ¶99.) In the non-limiting example depicted above, the Kumacheva droplet

generators 36 are positioned at the junctions of Modlin's unit cells 822. (Ex. 1004 ¶62; Ex. 1017 pp. 16-19; Ex. 1005 ¶¶208-214; Ex. 1003 ¶99.) The microwell microfluidic well plate assembly 610 is placed in contact with Modlin's pressure manifold 754 which drives the fluids among the wells above ports 1-4 in each unit cell 822. (Ex. 1005 ¶¶15, 201, 208-214; Ex. 1003 ¶99.) It would have been obvious to provide the Combined System with a gasket to enable the pressure manifold to seals against the wells. (*Id.*)

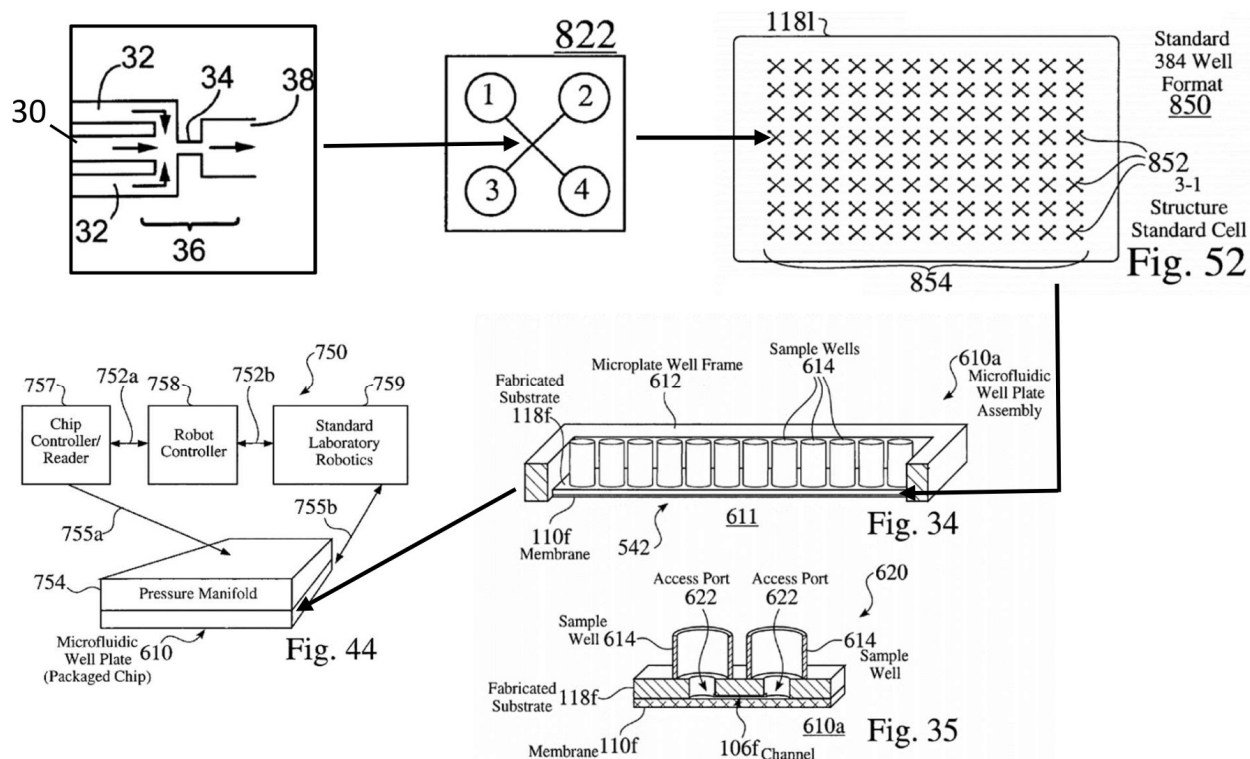
Claim 3 and 4 are thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶100.)

3. Dependent Claim 6

Claim 6 depends from claim 1 and recites that "the vacuum or pressure source is a pressure source configured to be connected operatively to input wells of the plate."

The Combined System includes a pressure manifold configured to operatively connect to wells and seal against the input wells. (Ex. 1003 ¶103.)

As discussed above in connection with claims 3 and 4, the Combined System's pressure manifold seals against the wells via a gasket. (*Id.*) In the illustrative Combined System depicted below, the manifold seals against both the input wells above ports 1-3 and the output well above port 4 of each unit cell. (*Id.*)



Claim 6 is thus rendered obvious by Kumacheva taken in view of Modlin.

(Ex. 1003 ¶104.)

4. Dependent Claim 8

Claim 8 depends from claim 1 and recites that the “plate includes a linear array of three or more emulsion production units.”

Kumacheva includes an array of three or more emulsion production units.

(Ex. 1003 ¶105.) Kumacheva discloses a quadra-droplet generator 10 having four parallel droplet or emulsion generators

20. (Ex. 1004 ¶¶61-65; Ex. 1017 pp. 16-

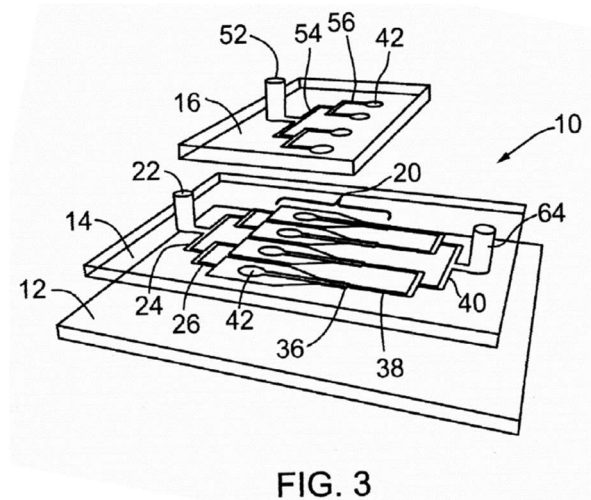
19.) “FIG. 3 shows a 3D illustration of

the quadra-droplet generator 10 (QDG) with four parallel flow-focusing devices

20.” (Ex. 1004 ¶63; Ex. 1017 p. 16 Ex.

1003 ¶105.)) Kumacheva thus meets

claim 8.



The Combined System also includes an array of three or more emulsion production units. (Ex. 1003 ¶¶106-107.) For example, in the illustrative Combined System depicted above, 96 unit cells (each containing an emulsion generator) are disposed on microfluidic well plate assembly 610. (*Id.*) The Combined System thus meets claim 8.

Claim 8 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶¶107-108.)

5. Dependent Claim 9

Claim 9 depends from claim 1 and recites that the “wells of the plate are spaced according to a well spacing of a standard microplate.”

Modlin teaches that the plate has wells aligned according to standard microplate spacing. (Ex. 1003 ¶110.) “Well frame assembly 700 is preferably fabricated with wells located on a **standard microplate pitch** such as 9 mm for a standard 96 well plate, 4.5 mm for a 384 well plate, 2.25 mm for a 1536 well plate and so on for other present and future standard plates.” (Ex. 1005 ¶186). “Microfluidic well plate assembly, 610, comprising a microfluidic chip according to aspects of the present teachings packaged in an **industry standard microplate format**, e.g., (FIGS. 33-37) designed to be compatible with industry standard physical conventions provides an interface 755b to standard laboratory robotics 759.” (Ex. 1005 ¶201, see also ¶45.) “An aspect of the present teachings is to intentionally provide compatibility with laboratory robotic standards enabling products made according to the present teachings to be readily used in conjunction with industry standard fluid dispensing, detection, and other robotics and automated processing equipment.” (*Id.*)

The Combined System also includes a plate with wells aligned according to standard microplate spacing. (Ex. 1003 ¶111.) For example, in the non-limiting example of the combined system depicted above, the 96 unit cells on microfluidic well plate assembly 610 are spaced according to the industry standard. (*Id.*)

Claim 9 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶¶112-113.)

6. Dependent Claims 10-11

Claim 10 depends from claim 1 and recites that the “second input well of each unit is disposed between the first input well and the output well of such unit.”

Claim 11 recites that “the first input well, the second input well, and the output well of each unit are arranged along a same line.”

Kumacheva teaches that the inputs and outputs are arranged in a line as recited in claims 10-11. (Ex. 1003 ¶¶114, 116.) “FIG. 2 depicts the fluid flow path in a single planar flow-focusing device shown generally at 20. Liquid A enters via opening 42 and travels downstream via the central microchannel 30 through orifice 34 to the outlet

microchannels 38. Liquid B enters via side microchannels 26 and travels through microchannel 32 through orifice 34 to the outlet microchannels

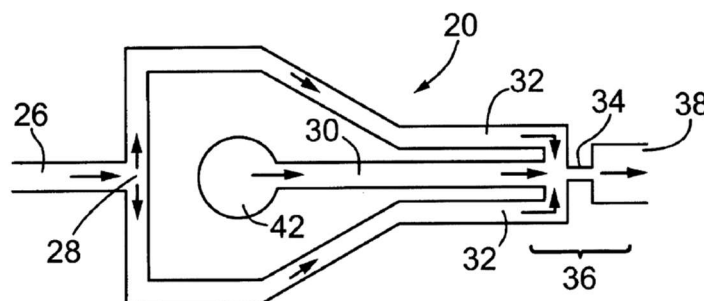
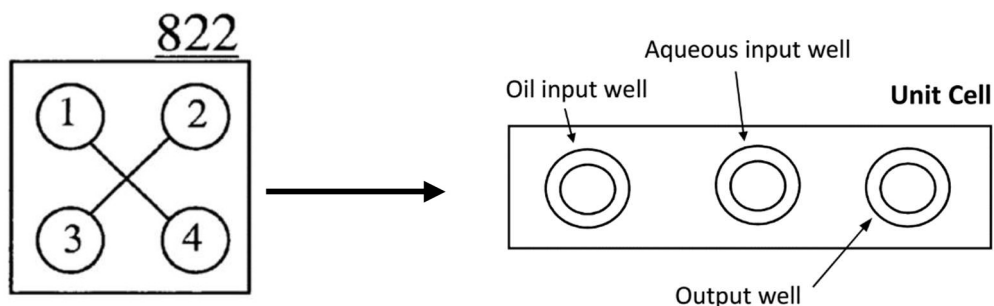


FIG. 2

38.” (Ex. 1004 ¶62; Ex. 1017 pp. 16-19.) According to Kumacheva, “[a] 2 wt % solution of a nonionic surfactant Span 80 in a light mineral oil was used as a continuous phase (introduced as liquid B).” (Ex. 1004 ¶70; Ex. 1017 p. 19.) Kumacheva thus teaches that the input for the dispersion phase (second well) is

positioned between the input for the continuous phase (first well) and the output. (Ex. 1003 ¶¶114, 116.)

It would have been obvious to configure the Combined System such that the input well for the dispersion phase is positioned between and along the same line as the input well for the continuous phase and the output well. (Ex. 1003 ¶¶114, 116.) This modification of the Combined System is illustrated below. (Ex. 1003 ¶160.) The 4-well unit cell 822 in the Combined System is replaced with a 3-well unit cell. (*Id.*) Although not required by claims 10-11, this modified unit cell also has wells positioned at industry standard spacing.



A skilled artisan would have seen various reasons to make this modification. (*Id.* ¶¶114, 116.) Modlin teaches that “[u]nit cells such as those depicted and explained in FIGS. 45-68 can be arranged, re-configured, and modified to implement a large variety of proffered embodiments to support many types of chemical, biochemical, and biological assays in industry standard microplate and microscope formats as well as in non-industry standard formats.” (Ex. 1005 ¶235.) In Figs. 62-68, Modlin shows various unit configurations in

which the unit cells include input and output wells arranged along the same line. (*Id.* ¶¶225-234.) Regarding the Combined System, a skilled in the art would have been motivated to configure the unit cells to correspond generally to the layout of the Kumacheva flow-focusing device, wherein a single input for the dispersion phase is positioned between a single input for the continuous phase and a single output. (Ex. 1003 ¶¶114, 116.) Having a single input well for the continuous phase in each unit cell reduces the number of manifold-to-well seals and thus not only simplifies the instrument but also reduces the risk of leaks. (*Id.*) Given that the input and output wells are substantially larger than the microchannels, the number and positioning of the input and output wells or ports is the primary factor controlling how closely the microfluidic circuits may be spaced. (*Id.*) For the most compact arrangement, a skilled in the art would locate the dispersion phase well (second input well) between the continuous phase well (first input well) and the output well, as recited in claim 10-11. (*Id.*)

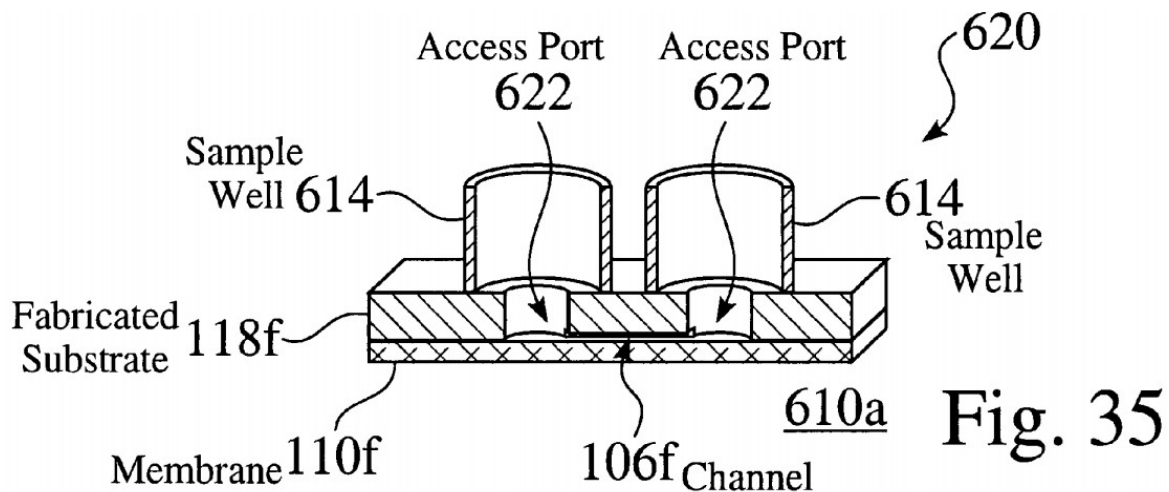
In the Combined System, therefore, it would have been obvious to provide a unit cell arrangement that generally corresponds to the Kumacheva FFD layout, *i.e.*, the dispersion phase input well would be positioned between the continuous phase input well and the output well, as recited in claims 10-11. (Ex. 1003 ¶¶114, 116.)

Claims 10-11 are thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶¶115, 117.)

7. Dependent Claim 12

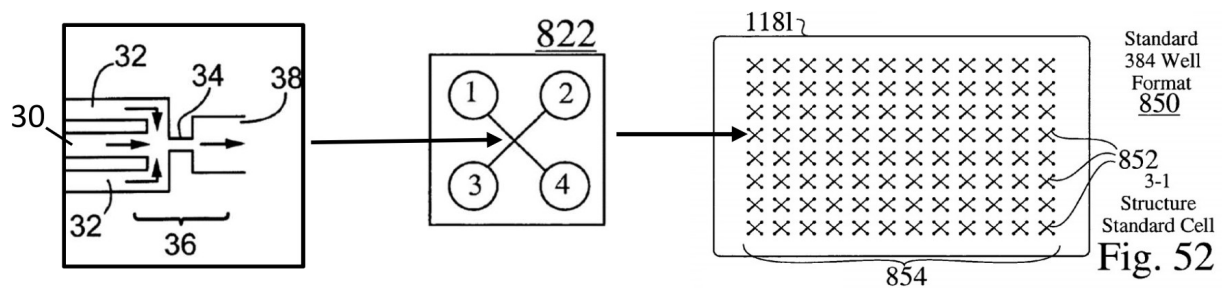
Claim 12 depends from claim 1 and recites that “each channel of the set of channels of each unit extends to the channel junction of such unit from a bottom region of a well and not a top region of the well.”

Modlin teaches that the channels extend from a bottom region of a well and not a top region of the well. Modlin teaches that the unit cells 820/822 include channels 106 extending from the base of the wells 614 as depicted in Fig. 35, reproduced below. (Ex. 1005 ¶¶175-180; Ex. 1003 ¶120.)



In the Combined System, this channel/well configuration is preserved, such that each channel extends to the channel junction of such unit from a bottom region of the well and not a top region of the well. (Ex. 1003 ¶¶120-121.)

As explained above, in the Combined System the parallel emulsion generator units of Kumacheva are modified according to the microplate well configuration of Modlin. *Id.* In the non-limiting example depicted below, the Kumacheva droplet generators 36 are positioned at the junctions of Modlin's unit cell 822. (Ex. 1004 ¶62; Ex. 1017 pp. 16-18; Ex. 1005 ¶¶208-214; Ex. 1003 ¶120.) The unit cells have the structure shown in Fig. 35, reproduced above. (Ex. 1003 ¶120.)



Claim 12 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶122.)

8. Dependent Claim 13

Claim 13 depends from claim 1 and recites that “wherein the plate includes an upper member attached to a lower member, wherein the upper member forms side walls of the wells of each unit and also forms top and side walls of each channel of the set of channels of each unit, and wherein the lower member extends under each well and channel of the unit to form a bottom wall of such well and channel.”

Modlin teaches that the channels and wells are formed in a substrate and that the bottom walls of those structures are provided by a lower member, as

recited in claim 13. Modlin teaches that the unit cells 820/822 include channels 106 formed in substrate 118 and a membrane 110 forming the bottom of the channels 106, as depicted in Fig. 35, reproduced at right. (Ex. 1005 ¶¶175-180;

Ex. 1003 ¶124.) Accordingly, the plate includes an upper member (substrate 118 (including wells 614/622)) attached to a lower member (membrane 110), wherein

the upper member forms side walls of the wells (614) of each unit and also forms top and side walls of each channel (106) of the set of channels of each unit,

and wherein the lower member (110) extends under each well (614/622) and channel of the unit to form a bottom wall of such well and channel as recited in claim 13. (Ex. 1003 ¶125.)

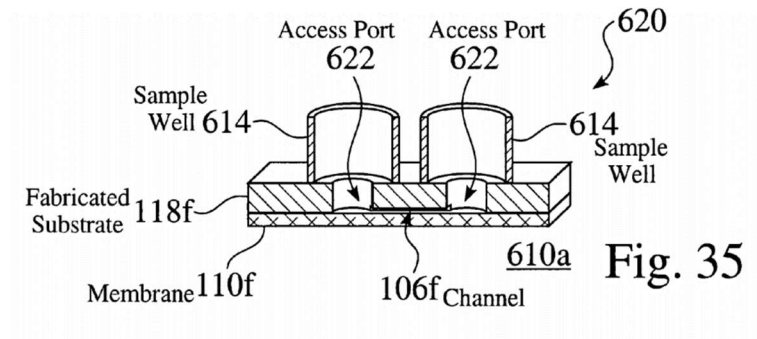


Fig. 35

In the combined system of Kumacheva and Modlin, this channel/well configuration is preserved, thus meeting the recitations of claim 13. (Ex. 1003 ¶125.) This aspect of the Combined System is discussed above in connection with claim 1.

Claim 13 is thus rendered obvious by Kumacheva taken in view of Modlin.
(Ex. 1003 ¶126.)

9. Dependent Claim 14

Claims 14 depends from claims 1 and 13 and recites that “the upper member is formed of an injection-molded polymer.”

The specification does not identify any unexpected result associated with fabrication by injection molding. To the contrary, the specification merely states that the upper member “may be manufactured by any suitable method, such as by injection molding a thermoplastic material.” (Ex. 1001 at 60:28-29.)

As discussed above in connection with claim 13, Modlin teaches that the plate includes an upper member (substrate 118 including wells 614). (Ex. 1003 ¶127.)

Modlin teaches that injection molding may be advantageously used to fabricate the upper members of the plates. (*Id.*) “Manufacturing of the assemblies of the present teachings may be carried out by any number of microfabrication techniques that are well known in the art.” (Ex. 1005 ¶160, see also ¶¶131, 133.) “[F]or polymeric substrates, well known manufacturing techniques may also be used. These techniques include injection molding techniques or embossing or stamp molding methods . . .” (*Id.*) “It is to be

understood that the present teachings are not limited to fabrication by one or the other of these methods.” (*Id.*)

In the Combined System, a skilled artisan would have been strongly motivated to make the upper member (substrate 118 and wells 614) via injection molding as suggested by Modlin. (Ex. 1003 ¶128.) Injection molding was well-known to be an economical process and that a variety of thermoplastics having good optical and mechanical properties can be processed by injection molding to form the desired structures. (See Ex. 1028 at 1:34-41; Ex. 1003 ¶128.) Indeed, as early as the 1990s it was taught that “[m]icrochannel structures . . . are typically produced by injection molding using various thermoplastic polymers.” (Ex. 1028 at 1:34-41.) In 1998 Dr. Gandhi filed a patent application teaching improved methods for sealing injection molded microfluidic plates. (Ex. 1012 at 7:63-8:57; Ex. 1003 ¶128.) By 2008, “[p]olymers [had] assumed the leading role as substrate materials for microfluidic devices.” (Ex. 1041 p. 1; Ex. 1042.) “The big advantages of injection molding are the ability to form three-dimensional objects, which, in the case of microfluidic devices, means e.g. the integration of fluidic interconnects . . . or through-holes. Furthermore, the ejected part does not normally need additional mechanical process steps, thus reducing the production time further. Owing to the highly industrialized development of the process, a large

variety of equipment suppliers are available as well as automation solutions for large-volume manufacturing.” (*Id.* p. 12.)

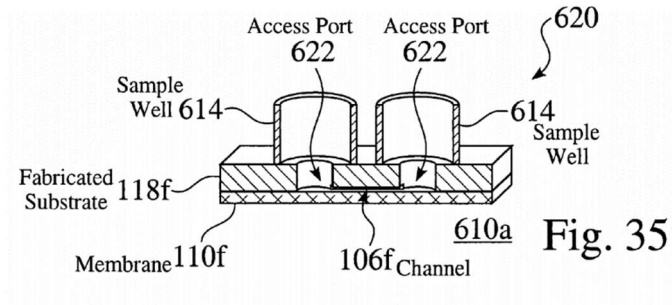
Because injection molding was one of the leading techniques for forming microfluidic plates at the time of filing, a skilled artisan would have had a strong expectation that the Combined System could be successfully fabricated by injection molding. (Ex. 1003 ¶128.) As of September 2008, skilled artisans understood that microfluidic chips would be manufactured according to a variety of well-known processes, including injection molding. (Ex. 1028 at 1:34-41, 10:33-39, 4:20-13:64; Ex. 1025 pp. 2-14; Ex. 1040; Ex. 1041 at 12; Ex. 1006 p. 2; Ex. 1032; Ex. 1003 ¶128.) Further, the plate or chip may be of an arbitrarily large size, which further simplifies the task of fabricating the upper members of the plates by injection molding. (Ex. 1003 ¶128.) Such would require no more than routine skill and would lead to predictable results. (*Id.*)

Claim 14 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶129.)

10. Dependent Claims 15

Claims 15 depends from claim 14 and recites that “each of the upper and lower members is formed by a respective, continuous piece of material.”

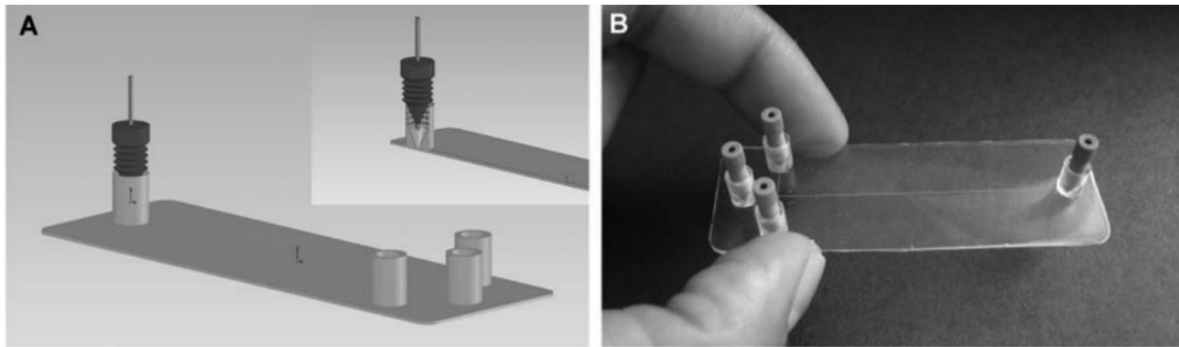
Modlin's lower member (membrane 110) is formed of a continuous piece of material. (Ex. 1003 ¶130.) The membrane 110 is continuous, as shown in Fig. 35, reproduced below, as well as Figs. 18-32, which illustrate the fabrication process. (Ex. 1005 ¶¶155-174; Ex. 1003 ¶130.) The lower member of the Combined System has this same structure and thus meets claim 15. (Ex. 1003 ¶131.)



Especially when the upper member (substrate 118 and wells 614) is formed by injection molding (as suggested by Modlin), it would have been obvious to fabricate Modlin's upper member from a single piece of material. (Ex. 1005 ¶160; Ex. 1003 ¶130.) Doing so would substantially simplify the manufacturing process and reduce cost. (*Id.*) Other advantages of injection molding are discussed above in connection with claim 14.

A skilled artisan would have considered it routine to fabricate the substrate 118 and wells 614 of the Combined System in a single piece by injection molding at the time of filing. (Ex. 1003 ¶131.) Such structures were commonly integrally formed by injection molding at the time of filing. (Ex. 1008 ¶72; Ex. 1011 ¶69; Ex. 1041 p. 12, Ex. 1003 ¶131.) For instance, in 2008 BioScale filed an application directed to a microfluidic plate with input wells 332 and output

wells 342, and explained that the entire body could be formed by injection molding. (Ex. 1008 ¶72; *see also* Ex. 1011 ¶69.) In 2006 Mair explained that the microfluidic chip shown below (including the upwardly extending inlets) was integrally molded from a single piece of plastic (excluding, of course, the threaded inserts). (Ex. 1047p. 6, Fig. 5; Ex. 1048; Ex. 1008 ¶72; Ex. 1011 ¶69.)



For these reasons, in the Combined System it would have been obvious to fabricate each of the upper member and the lower member from a continuous piece of material, thus meeting the recitations of claim 15. (Ex. 1003 ¶131.)

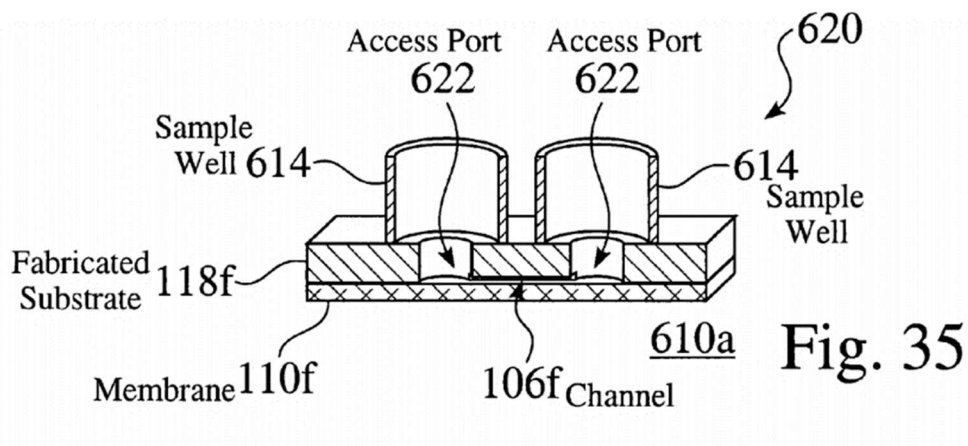
Claim 15 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶132.)

11. Dependent Claim 16

Claim 16 depends from claim 1 and recites “wherein the plate includes an upper member attached to a lower member, wherein the upper member includes upper and lower surfaces, wherein the upper member defines through-holes corresponding to the wells of each unit and extending from the upper surface to the

lower surface and also defines grooves corresponding to the set of channels of each unit and formed in the lower surface, and wherein the lower member is attached to the upper member at the lower surface to form a bottom wall below each through-hole and groove.”

Modlin teaches an upper member (substrate 118 and wells 614) having through holes 614/622 which extend therethrough and grooves that define channels 106 formed in the underside of the substrate. (Ex. 1003 ¶134.) Modlin teaches that the unit cells 820/822 include substrate 118 (upper member) including channels 106 formed in the lower surface thereof and through holes 614/622 defining wells, as depicted in Fig. 35 reproduced below. (Ex. 1005 ¶¶175-180; Ex. 1003 ¶134.)



Modlin teaches a lower member (membrane 110) having a surface that forms a bottom wall below each through-hole and groove. (Ex. 1003 ¶134.) As illustrated in Fig. 35, above, membrane 110 (lower member) forms the bottom of

the channels 106 and extending below the through holes 622, as depicted in Fig. 35 reproduced below. (Ex. 1005 ¶¶175-180; Ex. 1003 ¶134.)

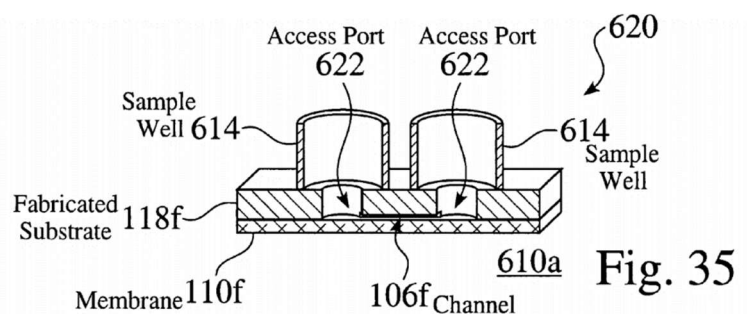
In the Combined System, the unit cells have this same structure, thus meeting the recitations of claim 16. (Ex. 1003 ¶134.)

Claim 16 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶135.)

12. Dependent Claim 17

Claim 17 recites that “the lower member is a sheet of material that is substantially thinner than the upper member.” The ’392 does not define what “substantially thinner” means; rather, the ’392 specification merely teaches that “[m]aintaining lower internal operating pressures rather than higher pressures also means that the cartridge can have . . . (c) thinner plates bonded to the microchannel side of the cartridge.” (Ex. 1001 at 88:57-63.)

Modlin’s membrane 110 is substantially thinner than the upper member (substrate 118 and wells 614), thus meeting the recitations of claim 17. Modlin teaches that the unit cells 820/822 include substrate 118 (upper member) and a substantially thinner membrane 110 (lower member) forming the bottom of the channels 106, as depicted in Fig. 35 reproduced



below. (Ex. 1005 ¶¶175-180; Ex. 1003 ¶136.) Modlin teaches that the membrane “may be fabricated with a thickness in the range of 10 to 100 microns or alternatively in the range of 1-50 microns.” Ex. 1005 ¶¶129, 322.) The upper member (substrate 118 and wells 614) must be at least several millimeters tall. (Ex. 1003 ¶136.) Assuming an upper member just 5 mm (5,000 microns) tall and a lower member (membrane) 50 microns thick, the lower member is **100X thinner** than the upper member, thus meeting the recitations of claim 17. (*Id.*)

In the Combined System, the unit cells have this same structure, thus meeting the recitations of claim 17. (Ex. 1003 ¶138.)

Claim 17 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶139.)

13. Dependent Claim 19

Claim 19 depends from claim 1 and recites that “the plate includes an upper member attached to a lower member to form an array of emulsion production units each configured to produce a separate emulsion, and wherein the lower member has an upper surface that is flat and that abuts a lower surface of the upper member to form a bottom wall of openings formed in the lower surface and corresponding to the wells and the channels of each unit.”

This claim recites features duplicative to those recited in claims 13 and 16 except that 19 further recites that each emulsion production unit is “configured

to produce a separate emulsion.” The discussion of claims 13 and 16 is incorporated by reference. In the Combined System described in connection with Claim 1, each unit cell has its own output well 2 which receives an emulsion from the droplet generator of that unit cell. (Ex. 1003 ¶¶140-141.) Each unit cells thus includes an emulsion production unit that produces an emulsion separate from the other unit cells, thus meeting the recitations of claim 19. (*Id.*)

Claim 19 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶142.)

14. Dependent Claim 20

Claim 20 depends from claims 1 and 19 and recites that “each of the upper and lower members is formed by a respective, continuous piece of material.”

The discussion of claim 15 is incorporated herein by reference. As explained therein, it would have been obvious to fabricate the upper and lower members of a respective, continuous piece of material.

Claim 20 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶¶143-146.)

15. Dependent Claim 21

Claim 21 depends from claim 1 and recites that “at least one first input well of each emulsion production unit is not shared with other emulsion production units of the plate.”

In the Combined System described in connection with claim 1, each unit cell includes an emulsion generator and each has an input well that is not shared with other emulsion generators in other unit cells. (Ex. 1003 ¶147.) The Combined System thus meets claim 21. (*Id.*)

Claim 21 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶148.)

B. Ground 2: Claims 2 and 5 Are Rendered Obvious by Kumacheva in View of Modlin and Further in View of Chien

1. Dependent Claim 2

Claim 2 depends from claim 1 and recites that “the vacuum or pressure source controls air pressure in wells to which the source is configured to be connected operatively.”

In the Combined System discussed above in connection with claim 1, the microfluidic well plate assembly 610 has an array FFD-containing unit cells and is placed in contact with Modlin’s pressure manifold 754. The manifold 754 provides pneumatic (air) pressure to drive the fluids among the microwells 1-4 in each unit cell 822. (Ex. 1005 ¶¶187-88, 202; Ex. 1003 ¶149.) However, because Modlin’s

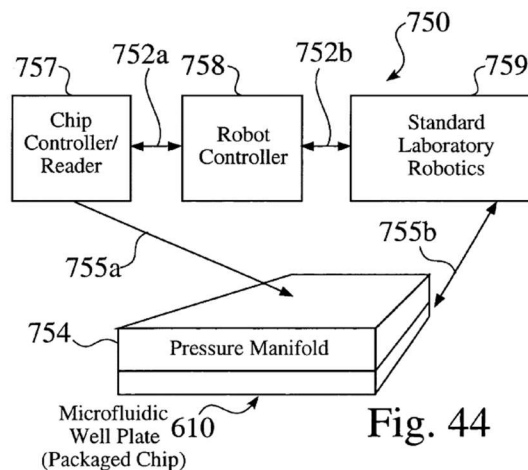


Fig. 44

discussion of the pneumatic control is abbreviated, Petitioner relies upon Chien for its teaching of using air pressure in the wells to drive the fluids. (Ex. 1003 ¶150.)

Chien teaches that it is preferable to drive fluids through microfluidic chips with a manifold that delivers air pressure to the headspace above the reservoirs of fluid stored in on-chip wells. (Ex. 1007 pp. 1-3.) Chien explained that this method substantially improves the accuracy of the fluid flow control relative to the previously reported approaches of pumping fluids directly into the microchannels from a source outside the chip or using on-chip micropumps. (*Id.*) The latter approaches were found to produce, relatively speaking, inconsistent or “erratic” results. (*Id.*)

A skilled artisan would have been strongly motivated to use Chien’s technique to improve upon the combined Kumacheva/Modlin device. (*Id.*; Ex. 1003 ¶151.) Modlin expressly suggests use of air pressure to drive the fluids in the wells, stating that “[a] plurality of connectors 712 are disposed within well frame body 710 to direct sources of externally generated and controlled **pneumatic** or hydraulic **pressure** to the **plurality of wells 728.**” (Ex. 1005 ¶187.) “Tapered plugs 714 or equivalent alternative means is provided to seal the well entrances allowing the externally controlled pressure **directed through connectors 712 to wells 728 to build up within the wells and provide a driving force** for flow within the channels of assembled chip 542.” (*Id.*) The build-up of pneumatic (as opposed to

hydraulic) pressure in the wells corresponds to the technique taught in more detail in Chien. (Ex. 1003 ¶151.) As noted by Chien, using this technique enables more precise and reproducible control of the fluid flows. (Ex. 1007 pp. 1-3; Ex. 1003 ¶151.)

Because each of the components of the Combined System were well known at the time of filing, a skilled artisan would have had a strong expectation that the Combined System could be modified as taught by Chien and would work as intended. (Ex. 1003 ¶152.)

Claim 2 is thus rendered obvious when Kumacheva and Modlin are taken further in view of Chien. (Ex. 1003 ¶153.)

2. Dependent Claim 5

Claim 5 depends from claim 1 and recites that “the vacuum or pressure source is a vacuum source configured to form a pressure sink at the output wells of the plate when the vacuum source is connected operatively to the output wells.”

Chien teaches creating a vacuum in the headspace above the reservoir of fluid stored in on-chip wells. (Ex. 1003 ¶154.) Chien teaches that an “eight-syringe pump system is used as [the] pressure or vacuum source. . . The incubation time is controlled by the vacuum applied to the waste well.”. (Ex. 1007 pp. 2, 3, 5.) The “waste well” is an output well. The ‘392 patent does not define “output.” However, dependent claim 18 recites the performance of a PCR reaction on the

device, after which the droplets would typically be optically analyzed (also on the device) and then discarded. Indeed, if the analytical test of interest has already been performed on the droplets before they arrive at the output well, as in Chien, then the droplets may be discarded. (Ex. 1039 at 21:13-38, 23:30-35; Ex. 1007 p. 5; Ex. 1003 ¶154.) The claim is open ended with respect to the output – the output well can collect either waste or droplets to be further analyzed. (Ex. 1003 ¶154.) Both are “output” in the context of the recited device. (*Id.*) Accordingly, Chien teaches application of a vacuum to create a pressure sink at an “output well” as recited in claim 5. (*Id.*)

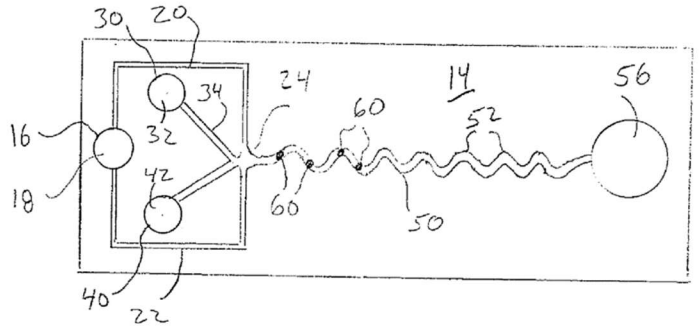
As explained above in connection with claim 2, one skilled in the art would have considered it obvious to use Chien’s technique to drive fluids from the wells and through the microchannels of plate in the Kumacheva/Modlin system. (Id.)

Claim 5 is thus rendered obvious when Kumacheva and Modlin are taken further in view of Chien. (Ex. 1003 ¶155.)

C. Ground 3: Claim 7 Is Rendered Obvious by Kumacheva in View of Modlin and Further in View of Hsieh

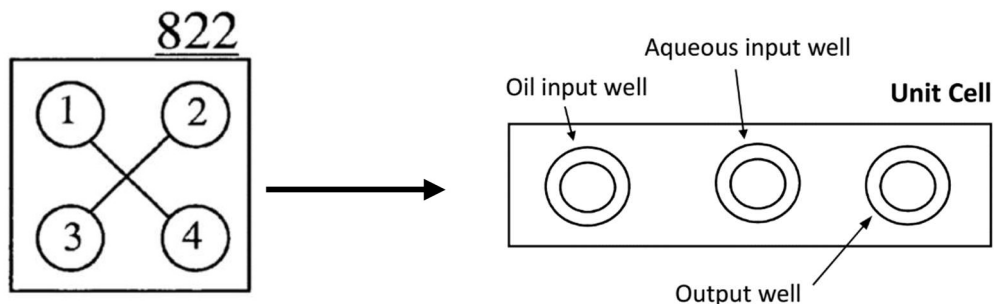
Claim 7 depends from claim 1 and recites that the “wells of each unit include only one first input well configured to hold the continuous phase, and wherein a pair of channels of the set of channels of each unit extend separately from one another to the channel junction of such unit from the only one first input well.”

Hsieh's channels extend separately to a droplet generation junction from one continuous phase inlet. Hsieh uses a “flow focusing” droplet generation approach (see Technical Background) in which opposing flows of oil pinch off droplets at a channel junction. Hsieh teaches that “substrate 14 includes a first inlet 16 that is configured to contain a carrier material 18 for the droplets 60. Generally, the carrier material 18 may include an immiscible continuous phase material such as, for instance, oil.” (Ex. 1019 ¶22.) “The **first inlet 16 is fluidically coupled to two separate channels 20, 22 that terminate in a junction or droplet generation region 24.**” (*Id.*) “[T]he droplet generation region 24 includes a pinch-off area or region that ‘pinches-off’ droplets generated from the streams flowing from the second inlet 30 and third inlet 40.” (*Id.*) Accordingly, Hsieh teaches (a) an emulsion production unit having only one first inlet 16 to hold the continuous phase (oil) and (b) a pair of separate channels 20, 22 that extend separately to the junction 24 from the inlet 16.



A skilled artisan would have been strongly motivated to modify the Combined System (Kumacheva/Modlin) to use a single inlet (as taught by Hsieh) to feed the continuous phase channels leading to the emulsion generator junction. (Ex. 1003 ¶160.) This modification of the Combined System is

illustrated below. (*Id.*) The 4-well unit cell 822 in the Combined System is replaced with a 3-well unit cell. (*Id.*)



A skilled artisan would have seen at least two reasons to make this modification. (*Id.*) **First**, as discussed above for claims 10-11, using a single input well for the continuous phase in each unit cell reduces the number of manifold-to-well seals and thus not only simplifies the instrument but also reduces the risk of leaks. (*Id.*) **Second**, doing so would save space and permit more droplet generators to be provided on a single chip. (*Id.*) Given that the input and output wells are substantially larger than the microchannels, the number and positioning of the input and output wells or ports is the primary factor controlling how closely the microfluidic circuits may be spaced. (*Id.*) For the most compact arrangement, a skilled in the art would use a single continuous phase well (first input well) as recited in claim 7. (*Id.*)

A skilled artisan would thus have considered it obvious to use a single input well to improve a similar system (the Combined System of Kumacheva and

Modlin) in the same way (to simplify the instrument and save space on the chip).

KSR, 550 U.S. at 415-421 (2007) (Ex. 1003 ¶¶160-161.)

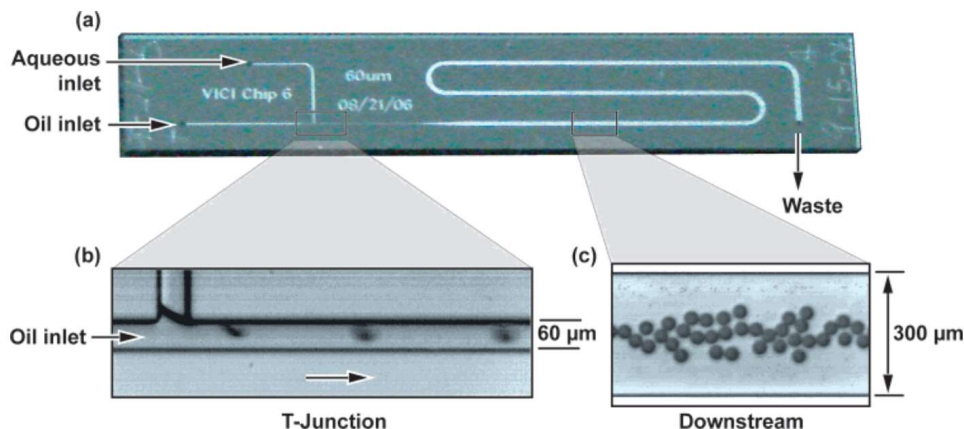
In light of the level of skill of art, a skilled artisan would have found it routine to make the foregoing combination (yielding the claimed limitation). (Ex. 1003 ¶161.)

D. Ground 4: Claim 18 Is Rendered Obvious by Kumacheva in View of Modlin and Further in View of Beer

Claim 18 depends from claim 1 and recites that “the first input well of a unit contains a nonaqueous continuous phase, wherein the second input well of such unit contains an aqueous phase configured for PCR amplification, and wherein the output well of such unit contains an emulsion including droplets of the aqueous phase disposed in the nonaqueous continuous phase.” Claim 18 is rendered obvious by Kumacheva and Modlin taken further in view of Beer. (Ex. 1003 ¶¶162-166.)

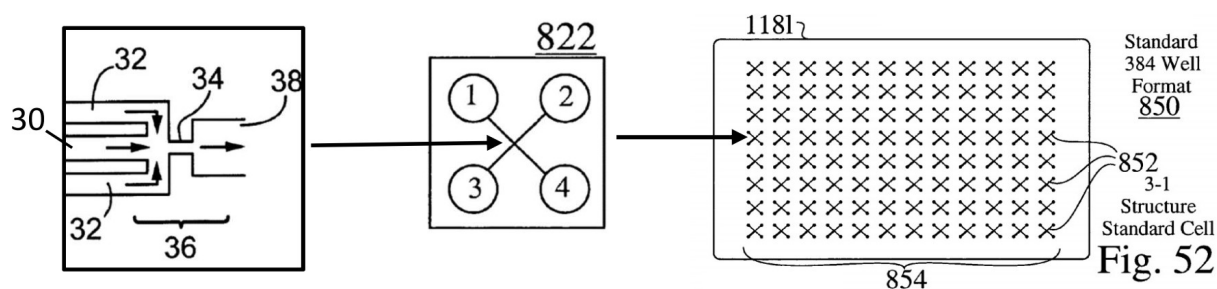
Beer teaches performing PCR in droplets formed with microfluidic emulsion generators. “To generate **water-in-oil (w/o) microdroplets**, we utilized a chip (Figure 1a) with hydrophobic channel surfaces and a shearing cross-flow Tjunction.” (Ex. 1034 p. 2.) “Two infusion syringe pumps (KD Scientific) independently drove the **aqueous and oil (M8662, Sigma-Aldrich) streams** at predetermined flow rates of 2.3 and 0.3 mL/h, respectively.” (*Id.*) “A **mixture of**

nucleic acid sample and PCR reagents was injected into the aqueous stream and delivered to the chip.” (*Id.*)



As discussed above in connection with claim 2, a “waste” well is an output well. That discussion is incorporated herein by reference.

When the Combined System of claim 1 is used to perform PCR as taught by Beer the Combined System meets claim 18. (Ex. 1003 ¶163.) In the illustrative combined system depicted below, oil is added to the first input well (1, 4), aqueous PCR reagents are added to the second input well (3), and the resulting emulsion is collected in the output well (2) of the combined system, thus meeting the recitations of claim 18. (*Id.*)



One skilled in the art would have been motivated to use the Combined System to perform PCR as taught by Beer and in accordance with claim 18. (Ex. 1003 ¶¶164-165.) Kumacheva expressly suggests using the device to perform PCR by noting that “[m]ultichannel microfluidic devices have been used for DNA separation, **parallel PCR assays**, detection of enzymatically-generated fluorescence and linear temperature gradients, capillary electrophoresis for immunoassays, and chiral separation.” (Ex. 1004 ¶14; Ex. 1017 pp. 9-10.) Combining the Kumacheva/Modlin system with Beer would provide a PCR instrument that provides “a level of control over microdroplet compartmentalization not achievable by ‘shake-and-bake’ methods.” (Ex. 1034 p. 2.) Beer also teaches that his method allows “detection of a single copy of nucleic acid at significantly reduced cycle thresholds and will benefit from the high-throughput and low reagent usage architecture that on-chip processes provide.” Accordingly, a skilled artisan would have been motivated to use the technique taught in Beer (PCR in picoliter sized droplets) to improve a similar device (the Kumacheva/Modlin system) in the same way (providing improved control and detection). *KSR*, 550 U.S. at 415-421 (2007).

In light of the level of skill of art, a skilled artisan would have found it routine to make the foregoing combination (yielding the claimed limitation). (Ex. 1003 ¶166.)

E. Ground 5: Claims 12-17 and 19-20 Are Rendered Obvious by Kumacheva in view of Modlin and Further in view of Soane

Claims 12-17 and 19-20, which depend directly or indirectly from claim 1, are rendered obvious by Kumacheva in view of Modlin and further in view of Soane.

Soane teaches “[m]ethods for fabricating enclosed microchannel structures.” (Ex. 1028, Title.) “The microchannel structures are constructed of a base plate and a cover . . . [these microchannels] are enclosed by bonding the planar surfaces of the cover and the base plate together.”

(*Id.* Abstract.) Shown in Fig.

6 (right) is “an assembled microchannel device 10 made

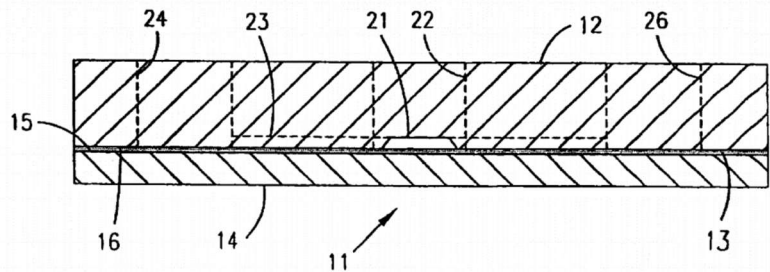


FIG. 6

by bonding a base plate 12 . . . to a cover 14.” (*Id.* at 5:35-38.) “Base 12 has a planar surface 13 in which a microchannel structure is formed, including intersecting linear microchannels 21, 23. At the ends of the channels holes 22, 24, 26, 28 are bored through, to provide reservoirs for fluids to be moved within the channels.” (*Id.* at 5:45-49.) “Cover 11 has a generally planar surface 15, apposable onto the channel-bearing surface 13 of base plate 12, onto which a thin film 16 of a bonding material is applied. Microchannel device 10 is formed by opposing the surfaces 13, 15 with the bonding material between them. As a result, the

microchannels 21, 23 are closed, having three walls formed in the base plate surface 13, and a fourth wall formed by the cover 11, with the bonding material film 16 constituting the surface of the fourth microchannel wall.” (*Id.* at 5:55-64.) “Reservoirs formed as described above are open on a surface of the base plate opposite the surface apposed to the cover.” (*Id.* at 5:65-67.)

A skilled artisan would have been motivated to fabricate the Combined System of Kumacheva/Modlin using Soane’s methods. **First**, Soane teaches that his injection-molding based methods “would be much more economical, and therefore desirable” than other methods such as photolithography. (Ex. 1028 at 2:7-10.) Soane explains that “microchannel structures . . . are typically produced by injection molding using various thermoplastic polymers. Injection molding is an economical process, and a variety of thermoplastics having good optical and mechanical properties can be processed by injection molding to form the desired structures.” (*Id.* at 1:27-38.) **Second**, Soane demonstrated his methods created “polymeric microchannel structures . . . [w]ithout deformation, partial or complete clogging of the enclosed microchannels.” (*Id.* 13:42-49.) Accordingly, Soane permits the realization of the benefits of injection molding without any potential disadvantages which would prevent its use in the context of the Combined System. (Ex. 1003 ¶169.)

One skilled in the art would have had a reasonable expectation of success using the Soane method to fabricate the Combined System. (Ex. 1003 ¶170.)

Soane provides various working examples which could be directly applied to fabricate the Combined System. (*Id.*) In light of the level of skill of art, a skilled artisan would have found it routine to make the foregoing combination and would fully expect that the combination (yielding the claimed limitation) would work as expected (*Id.*)

1. Dependent Claim 12

The text of claim 13 is reproduced in Section VIII.A.7.

Soane teaches channels that extend to a channel junction from a bottom region of a well. As shown in Fig. 6 (right), “[b]ase 12 has a planar surface 13 in which a microchannel structure is formed, including intersecting linear

microchannels 21, 23. At the ends of the channels holes 22, 24, 26, 28 are bored through, to provide reservoirs

for fluids to be moved within the channels.” (Ex. 1028 at

5:45-49, *see also* 5:50-67.) As

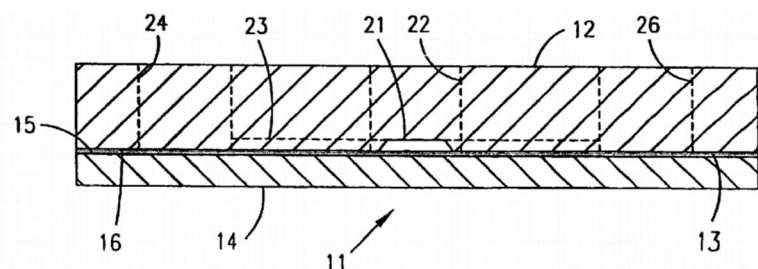


FIG. 6

depicted in Fig. 6, these microchannels 21, 23 extend from the bottom (not top) regions of these reservoirs 22, 24, 26, thus meeting the recitations of claim 12.

(Ex. 1003 ¶¶172, 174.)

2. Dependent Claim 13

The text of claim 13 is reproduced in Section VIII.A.8.

Soane teaches an upper member (base plate 12) forms side walls of the wells (holes 24, 26) of each unit and also forms top and side walls of each channel (channels 21/23) and the lower member (film 16 or, alternatively, film 16 and cover 14) extending under each well and channel of the unit to form a bottom wall of such well and channel. (Ex. 1003 ¶175.) “Cover 11 has a generally planar surface 15, apposable onto the channel-bearing surface 13 of base plate 12, onto which a thin film 16 of a bonding material is applied. Microchannel device 10 is formed by apposing the surfaces 13, 15 with the bonding material between them.” (Ex. 1028 at 5:55-60.) “As a result, the microchannels 21, 23 are closed, having **three walls formed in the base plate surface 13, and a fourth wall formed by the cover 11, with the bonding material film constituting the surface of the fourth microchannel wall.**” (Ex. 1028 5:55-64, see also Examples 1-8 at 9:65-13:7.) The Soane structure thus meets claim 13. (Ex. 1003 ¶175.)

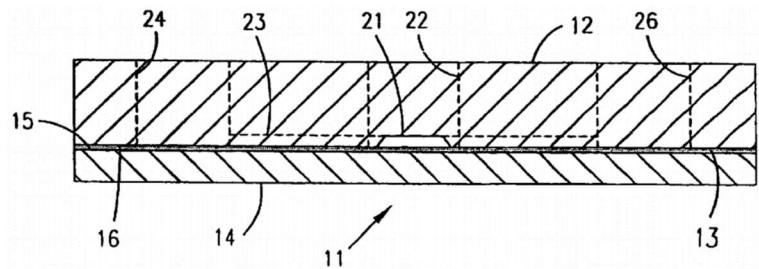


FIG. 6

3. Dependent Claim 14

The text of claim 14 is reproduced in Section VIII.A.9.

Soane teaches an upper member (base plate 12) formed of an injection molded polymer. “Microchannel structures . . . are typically produced by injection molding using various thermoplastic polymers.” (Ex. 1028 at 1:27-35.)

“[I]njection molding techniques were used to prepare a microchannel base plate of an acrylic polymer (AtoHaas, PlexiglasTMV825NA-100).” (Ex. 1028 at 10:36-40, see also 11:27-31, 12:7-13:7.) The Soane base plate 12 thus meets claim 14. (Ex. 1003 ¶¶176-177.)

4. Dependent Claim 15

The text of claim 15 is reproduced in Section VIII.A.10.

Soane discloses that each of the base plate 12 (the upper member) and the bonding material film 16 (the lower member) is formed by a continuous piece of material. “In general, the microchannel structures according to the invention are constructed of two parts, each having at least one generally planar surface, sealed together so that the generally planar surfaces are apposed. One part is referred to as a base plate, and the other is referred to as a cover.” (Ex.

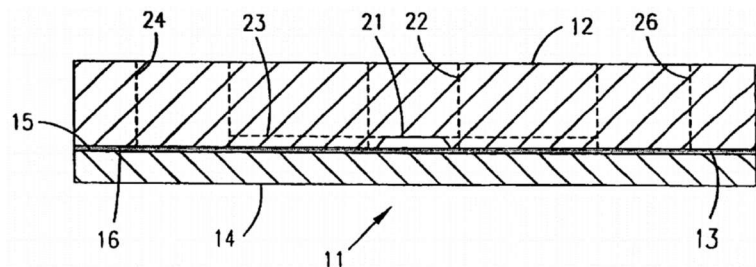


FIG. 6

1028 at 4:59-66.) The base plate 12 is formed by injection molding, which results in a plate made from a single, continuous piece of material. (Ex. 1028 at 10:36-40, see also 11:27-31, 12:7-13:7; Ex. 1003 ¶178.) “The cover [11] may be a more or less rigid plate, or it may be a film . . . [and] may be fabricated from a single material or be fabricated as a composite material.” (Ex. 1028 at 4:66-5:7.) In Example 2, for instance, the cover 11 is a continuous Mylar film coated with an adhesive such that the adhesive layer may be considered the lower member. (*Id.* at 10:29-57; see also 5:55-64.) In Fig. 6, the lower member is depicted as “bonding material film 16.” (*Id.*) The base plate 12 and bonding material film 16 of Soane are each made of a continuous piece of material and thus meet claim 15. (Ex. 1003 ¶179.)

5. Dependent Claim 16

The text of claim 16 is reproduced in Section VIII.A.11.

Soane includes an upper member (base plate 12) having an upper surface defining through-holes (22, 24, 26) corresponding to the wells extending to its lower surface which has grooves (21,23) corresponding to the set of channels, and a lower member (film 16 or, alternatively, film 16 and cover 14) that forms a bottom wall below each through-hole

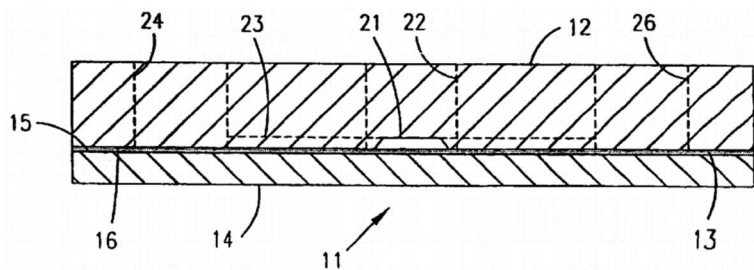


FIG. 6

and groove. (Ex. 1028 at 5:45-64, *see also* Examples 1-8 at 9:65-13:7. Ex. 1003 ¶181.) The base plate 12 and bonding material film 16 of Soane thus meet claim 16. (Ex. 1003 ¶¶181-182.)

6. Dependent Claim 17

The text of claim 13 is reproduced in Section VIII.A.12.

Soane teaches that the lower member (film 16 or, alternatively, film 16 and cover 14) can be a sheet of material that is substantially thinner than the upper member (base 12). In Fig. 5-6 of Soane, the bonding material film (lower member) is depicted as being substantially thinner than the base plate 12. (Ex. 1028 at 4:47- 6:30; Ex. 1003 ¶183.)

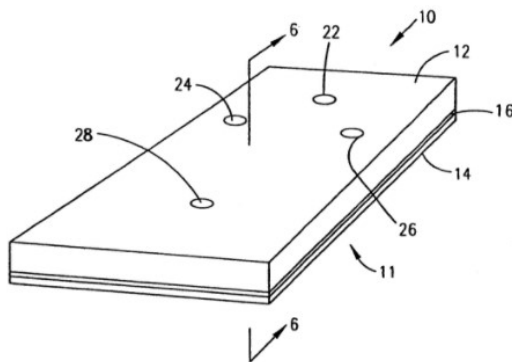


FIG. 5

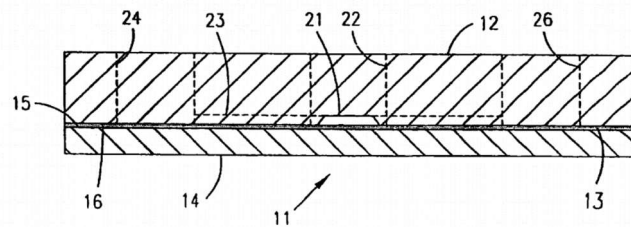


FIG. 6

As to the lower member (bonding material 16) Soane teaches that “[i]n practice, generally, the bonding material usually is applied to a thickness at least about 0.5 μm , in some embodiments at least about 1 μm , and in still other embodiments at least about 2 μm .” (Ex. 1028 at 6:26-30.) As to the base plate 12 into which the

channels are formed, Soane teaches that “the thickness of the polymeric material [in which the channels are formed] will be at least about 1 μm , usually at least about 5 μm , and more usually at least about 50 μm , where the thickness may be as great as 5 mm or greater.” (Ex. 1028 at 4:47-51.) Soane thus teaches that the bonding material 16 is usually on the order of 1 μm whereas the base plate 12 is usually on the order of at least 50 μm .

In the alternative, if bonding material 16 and cover 14 are together considered the lower member, Example 2 teaches that the cover 14 may be a 2 mil (50.8 micron) sheet of Mylar. (Ex. 1028 at 10:45-50.) The lower member would thus be 51 μm and Soane teaches that the base plate 12 (upper member) would be 5 mm (5,000 μm) or greater.

Under either approach, Soane thus meets the recitations of claim 17.

7. Dependent Claim 19

The text of claim 19 is reproduced in Section VIII.A.13.

This claim recites features duplicative to those recited in claims 13 and 16 except that 19 further recites that each emulsion production unit is “configured to produce a separate emulsion.” The discussion of claims 13 and 16 is incorporated by reference. In the Combined System described in connection with Claim 1, each unit cell has its own output well 2 which receives an emulsion from the droplet generator of that unit cell. (Ex. 1003 ¶185.) Each unit cells thus

includes an emulsion production unit that produces an emulsion separate from the other unit cells, thus meeting the recitations of claim 19.

8. Dependent Claim 20

The text of claim 13 is reproduced in Section VIII.A.15.

The discussion of claim 15 is incorporated herein by reference. As explained therein, it would have been obvious to fabricate the upper and lower members of a respective, continuous piece of material.

For the foregoing reasons claims 12-17 and 19-20 are rendered obvious by Kumacheva and Modlin taken further in view of Soane. (Ex. 1003 ¶¶167-188.)

IX. SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS CANNOT OVERCOME THE OBVIOUSNESS GROUNDS

Petitioner is unaware of any objective indicia of nonobviousness that would overcome the obviousness grounds set forth above. Petitioner is not aware of any industry praise of the subject matter recited in the challenged claims. Neither Patent Owner's website nor its complaint in *Bio-Rad Laboratories, Inc., et al. v. 10X Genomics, Inc.*, Case No. 3:17-cv-4339 (N.D. Cal.) assert that the '392 patent was praised in the industry. Nor does Patent Owner therein allege commercial success, copying, failure of others, unexpected results, long-felt need or industry acquiescence, much less attempt to establish any nexus between such objective

indicia and any novel aspect of the claimed subject matter. *Novartis AG v. Torrent Pharmaceuticals Ltd.*, 853 F. 3d 1316, 1331 (Fed.Cir. 2017).

X. CONCLUSION

For the foregoing reasons, claims 1-21 of the '392 patent recite subject matter that would have been considered obvious by a skilled artisan at the time of filing. Petitioner requests institution of an *inter partes* review to cancel those claims.

Respectfully submitted,

Date: December 14, 2017

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WORD COUNT CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing petition for *inter partes* review complies with 37 C.F.R. § 42.24 because it contains 13,474 words as measured by the word processing software used to prepare the document, including footnotes and the reproduction of the claim language but excluding the table of contents, mandatory notices under §42.8, certificate of service or word count, and appendix of exhibits.

Date: December 14, 2017

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CERTIFICATE OF SERVICE

The undersigned certifies service pursuant to 37 C.F.R. §§42.6(e) and 42.105(b) on the Patent Owner by USPS Priority Mail Express of a copy of this Petition for *Inter Partes* Review and supporting materials at the correspondence address of record for the '392 patent to:

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200 Pacific Building
520 SW Yamhill Street
Portland OR 97204

Dated: December 14, 2017

/Greg H. Gardella/

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