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Filed By: Greg H. Gardella, Reg. No. 46,045
Gardella Grace P.A.
455 Massachusetts Ave. NW, Suite 507
Washington, DC 20001
Tel: (703) 740-4540
Email: ggardella@gardellagrace.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.

Petitioner,

v.

BIO-RAD LABORATORIES, INC.

Patent Owner.

IPR2018-00432

U.S. Patent No. 9,126,160

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Petitioner, 10X Genomics, Inc. ("Petitioner") respectfully requests *inter partes* review ("IPR") of claims 1-21 of U.S. Patent No. 9,126,160 ("the '160 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 '160 patent (IPR2018-00433 and IPR2018-00434). 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

Lead Counsel	Back-up Counsel
Greg H. Gardella Reg. No. 46,045 Gardella Grace P.A. 455 Massachusetts Ave. NW Suite 507 Washington, DC 20001 Tel: (703) 740-4540 Email:ggardella@gardellagrace.com	Dianna Devore Reg. No. 42,484 Sally Brashears Reg. No. 38,087 Convergent Law Group LLP 20660 Stevens Creek Blvd Suite 381 Cupertino, CA 95014 Email: DDevore@convergentlaw.com

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 info@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 '160 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, only one of which was 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 '160 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 ¶40.) 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, 30-31[1]; Ex. 1003 ¶39.)

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 '160 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 not before the Examiner during prosecution.

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), published on July 27, 2001, is prior art to the '160 patent under 35 U.S.C. §102(b)

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[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.

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

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 '160 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 sixteen (416) references cited during *ex parte*

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[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.)

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 '160 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 '160 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 ¶53.) Additional training or study would substitute for work experience and additional work experience or training would substitute for formal education. (*Id.*)

As of September 2008, it was generally known in the art that pressure-driven microfluidic droplet/emulsion[3] generators were in widespread use for performing chemical, biochemical and biological assays. (Ex. 1014 ¶¶3, 12, 15, 39, 70, 84, 103, 115, 290-292; Ex. 1015 at Fig. 2, ¶¶6, 50-55, 60-63, 114-115; Ex. 1016 pp. 1-3; Ex. 1013; Ex. 1031 pp. 1-2; Ex. 1024; Ex. 1004 ¶¶14, 61-65; Ex. 1017 pp. 9-10, 16-19; Ex. 1021, Fig. 3, ¶¶58, 64, 66; Ex. 1022, Fig. 2, ¶¶67-68; Ex. 1003 ¶¶12-22.) It was also known that such microfluidic circuits were commonly arranged in parallel to increase throughput. (Ex. 1005 ¶¶ 151-53, 209-35; Ex. 1019 ¶¶5-13, 26,

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[3] The '160 patent broadly defines emulsion as "a composition comprising liquid droplets disposed in an immiscible carrier fluid, which also is liquid." (Ex. 1001 at 10:11-12.) The term "droplet generator" and "emulsion generator" are used interchangeably herein to refer to fluidic junctions which create droplets disposed in an immiscible carrier fluid. (Ex. 1003 ¶12.)

49-50, 83; Ex. 1029 ¶¶2, 8-13, 29-35, 44-52; Ex. 1009 at Abstract, ¶¶, 2, 5, 53, 57, 61, 65, 69, 78, Figs. 2A and 20; Ex. 1004 ¶¶2, 6-7, 11, 14, 18-21, 61-70; Ex. 1017 pp. 7-12, 16-19; Ex. 1008 at Fig. 2A and 3, ¶¶6, 54, 56, 63-65, 68; Ex. 1011 at Fig. 2A, 3, ¶¶5, 51, 53, 60-62, 65; Ex. 1021, Fig. 3, Fig. 6, ¶¶92, 93, 239; Ex. 1031 p. 2; Ex. 1022, Fig. 2, ¶75; Ex. 1003 ¶¶22-31.) Further, it was generally known that microfluidic chips could be manufactured according to a variety of well-known processes including casting, injection molding, and compression molding. (Ex. 1028 at 1:34-41; 10:33-39; 4:20-13:64; Ex. 1025 pp. 23-35; Ex. 1040; Ex. 1006 p. 9; Ex. 1032; Ex. 1012 at 4:45-57, 7:52-62, 11:48-51; Ex. 1008 ¶72; Ex. 1011 ¶69; Ex. 1041 pp. 1, 12; Ex. 1042; Ex. 1003 ¶¶32-36.)

Each of these teachings are within the level of ordinary skill in the art. (Ex. 1003 ¶37.)

VI. OVERVIEW OF THE '160 PATENT

The '160 patent describes the alleged invention as comprising "a plate providing an array of emulsion production units…each including a set of wells" and "[e]ach set of wells, in turn, may include (1) at least one first input well to receive a continuous phase, (2) a second input well to receive a dispersed phase, and (3) an output well configured to receive from the site of droplet generation an emulsion of droplets of the dispersed phase disposed in the continuous phase."

(Ex. 1001 at 1:46-57.) Figures 4, 22, 23 and 24 (annotated with arrows below) are illustrative.

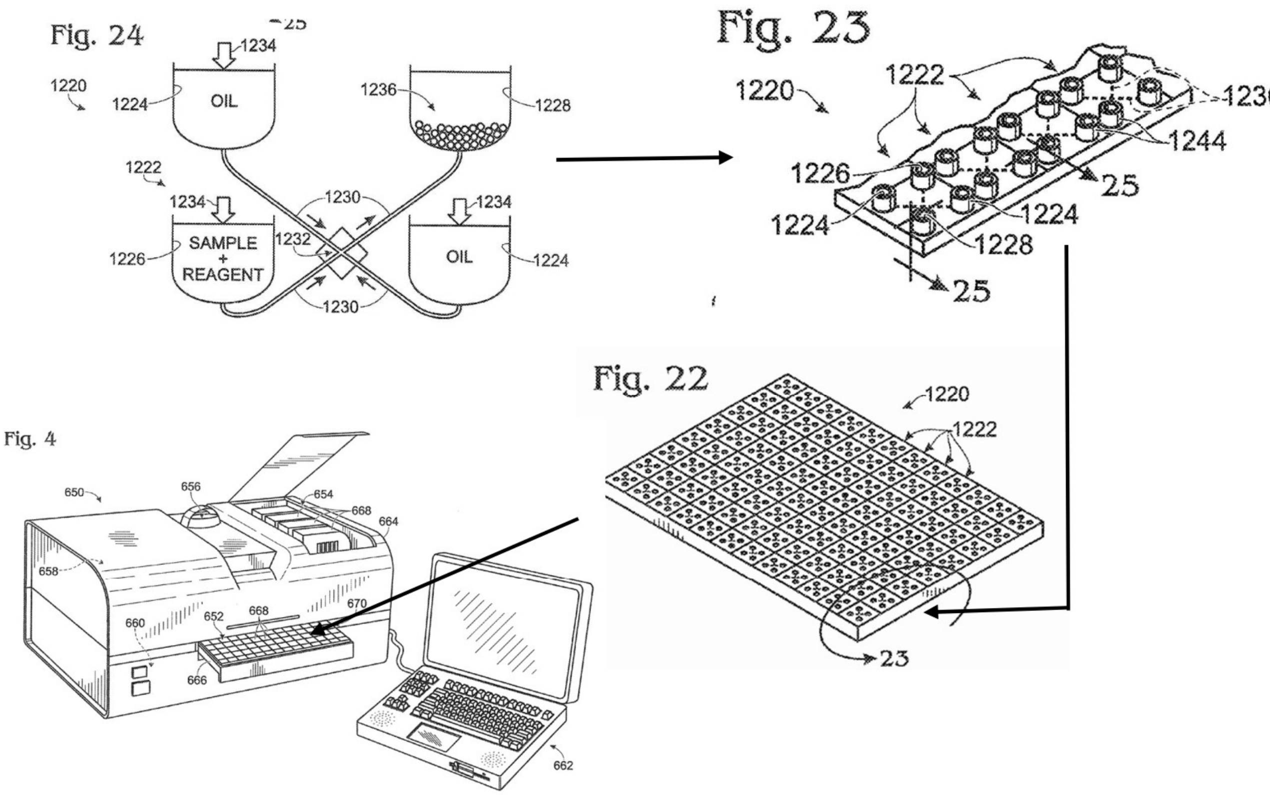


Fig. 4 shows that an instrument 650 receives plate 670 that includes reservoirs or wells 668 and a droplet generator. (*Id.* at 20:16-40.) Fig. 22 shows the plate and droplet generators. (*Id.* at 35:24-55.) Figure 23 is a close-up of area 23 of Fig. 22. (*Id.*) Figure 24 illustrates the four-port droplet 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 '160 Patent

The '160 patent claims priority to various provisional applications, the first of which was filed September 23, 2008. In the pending ITC proceeding, Patent Owner alleged that the claims of the '160 patent are entitled to the benefit of the date of U.S. Provisional Application No. 61/271,538, filed July 21, 2009. (Ex. 1027 p. 2)

Because each of the prior art references presented herein is prior art even to the '160 patent's earliest claimed priority date, Petitioner does not address whether the '160 patent is entitled to its claimed priority dates. Petitioner reserves the right to challenge the priority claims of the '160 patent.

B. Summary of the Prosecution History

During prosecution, the Examiner raised only a single prior-art rejection against the independent claim. The rejection was an anticipation rejection based on Pollack et al. 2008/0038810. (Ex. 1002 pp. 138). 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.*)

However, Pollack's droplet generator is neither the T-junction nor the cross-junction described in the prior art emulsion generator references cited in Section V, above. 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 at ¶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 set of channels forming a channel junction and droplet formation at the channel junction formed by the inlet channels and the outlet channel. (Ex. 1002 pp. 118-119, 138-139.) The Examiner allowed the claims on this basis. The reasons for allowance read as follows:

> [T]he prior art fails to teach or fairly suggest a plate with a plurality of emulsion production units where the droplets are formed at the channel junction of at least two input channels and an output channel where these limitations in combination with the claim as a whole.

(Ex. 1002 pp. 37.)

The Examiner did not discuss any of the numerous prior art references discussed above in Section V that disclose pressure-driven droplet generators in which two immiscible fluid flows intersect at a junction to form droplets.

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 '160 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, 3-13, 15-16, 18 and 20-21 Are Rendered Obvious by Kumacheva in View of Modlin

Claims 1, 3-13, 15-16, 18 and 20-21 are rendered obvious by Kumacheva in view of Modlin. Neither Kumacheva nor Modlin were before the Examiner. As depicted below, the preferred embodiment of the '160 patent corresponds closely to the combined system of Kumacheva and Modlin.

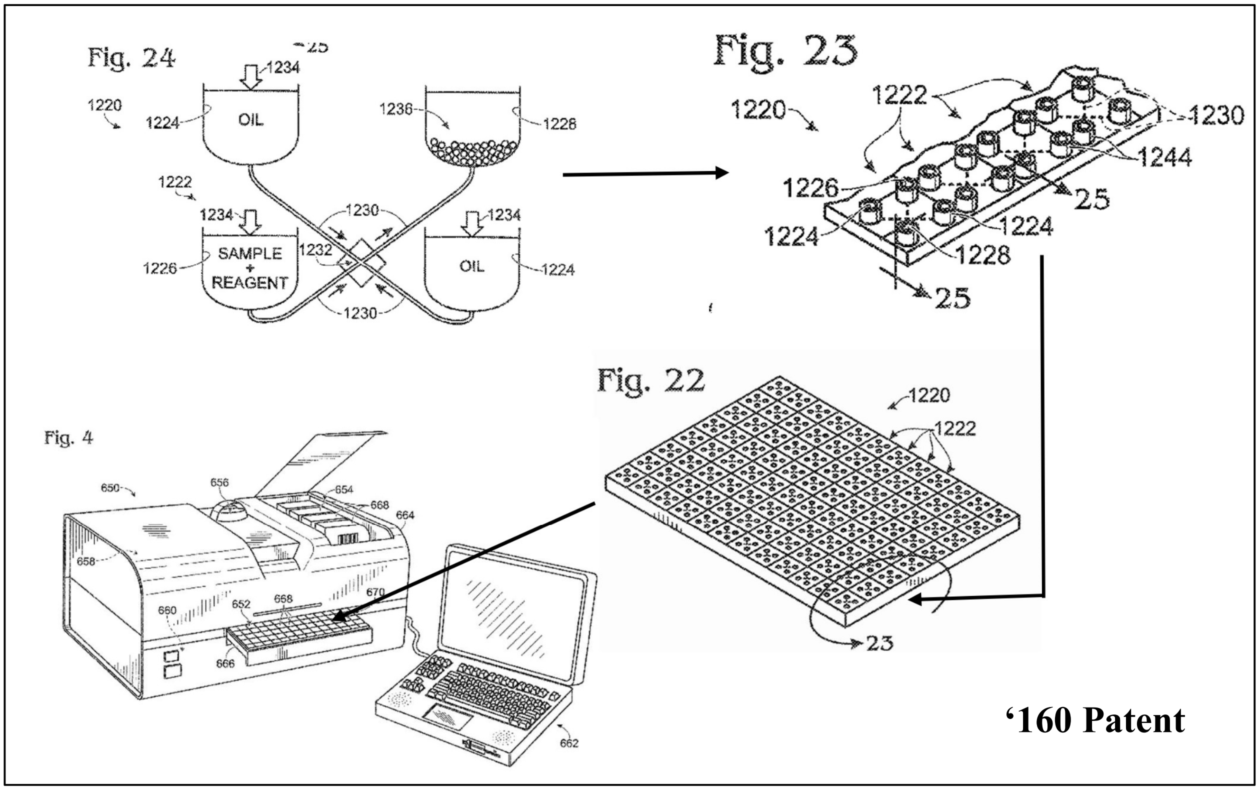
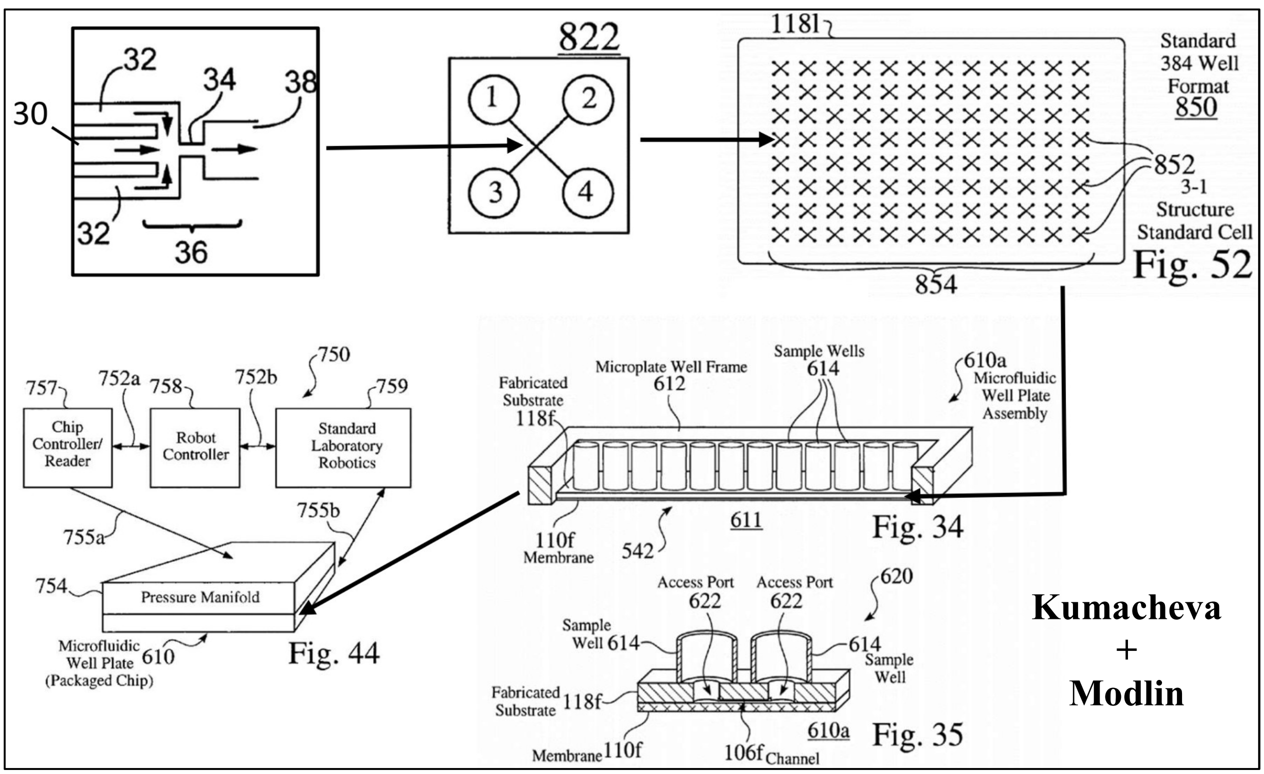


Fig. 24
OIL
SAMPLE + REAGENT
OIL
Fig. 23
Fig. 22
Fig. 4
'160 Patent


822
Standard 384 Well Format 850
852 3-1 Structure Standard Cell
Fig. 52
854
Chip Controller/ Reader
Robot Controller
Standard Laboratory Robotics
Pressure Manifold
Microfluidic Well Plate 610 (Packaged Chip)
Fig. 44
Fabricated Substrate 118f
Microplate Well Frame 612
Sample Wells 614
610a Microfluidic Well Plate Assembly
110f Membrane
Fig. 34
Access Port 622
Access Port 622
Sample Well 614
614 Sample Well
Fabricated Substrate 118f
Membrane 110f
106f Channel
Fig. 35
Kumacheva
+
Modlin

1. <u>Independent Claim 1</u>

Kumacheva and Modlin render independent claim 1 of the '160 patent obvious. (Ex. 1003 ¶55.)

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 pp. 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. 1003 ¶56).

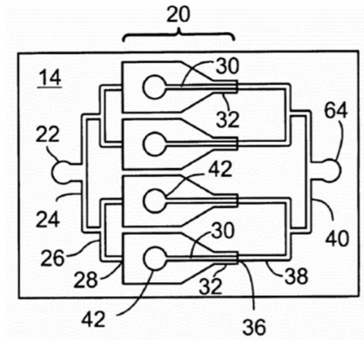
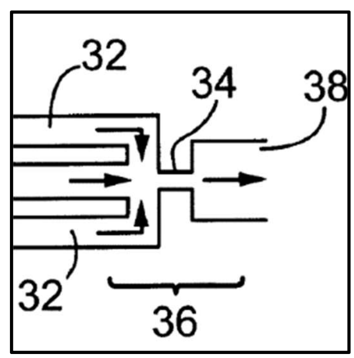


FIG. 4



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 ¶57.) 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 ¶57.)

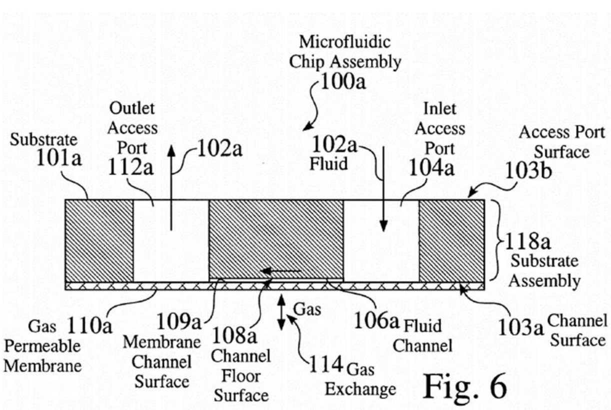


Fig. 6

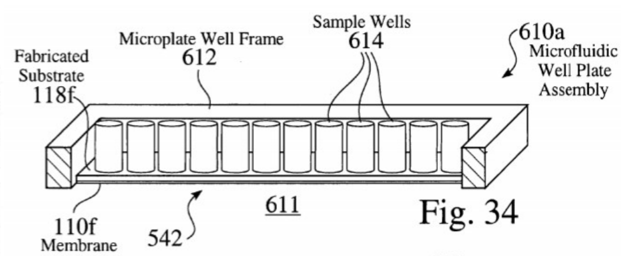


Fig. 34

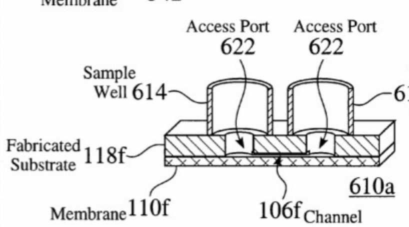


Fig. 35

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.)

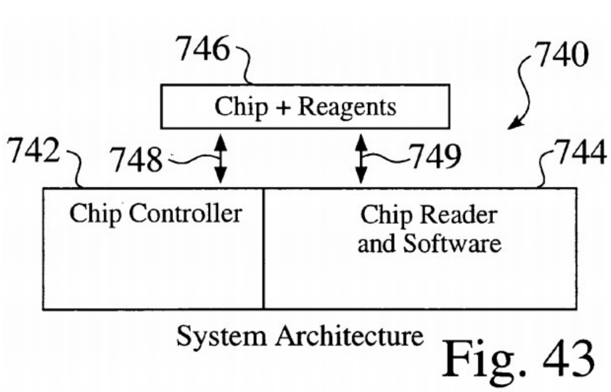


Fig. 43

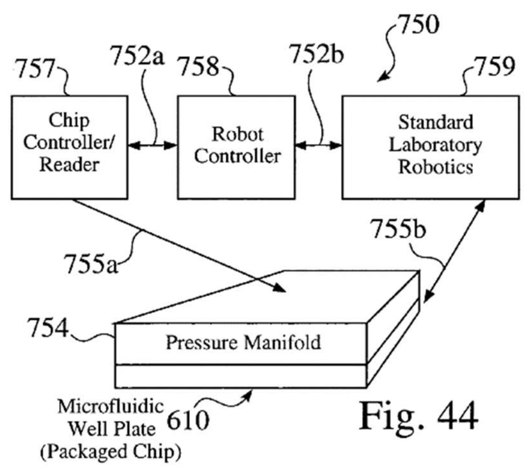


Fig. 44

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)[4].) 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.)

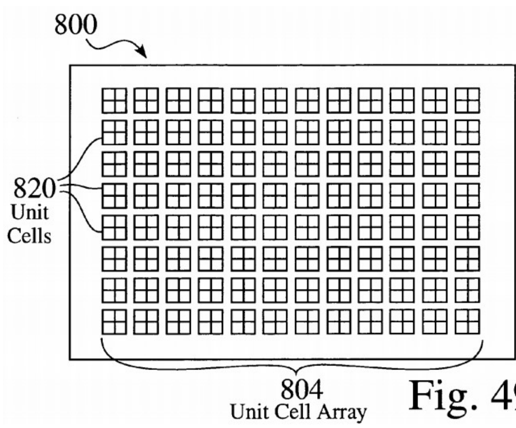


Fig. 49

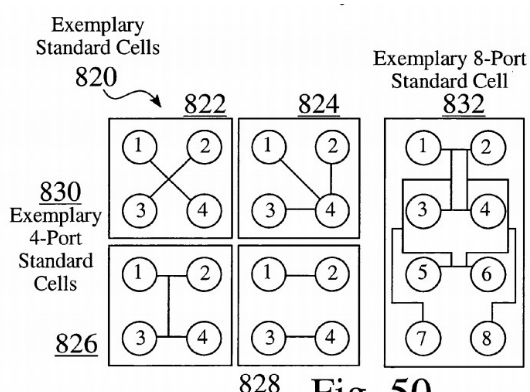
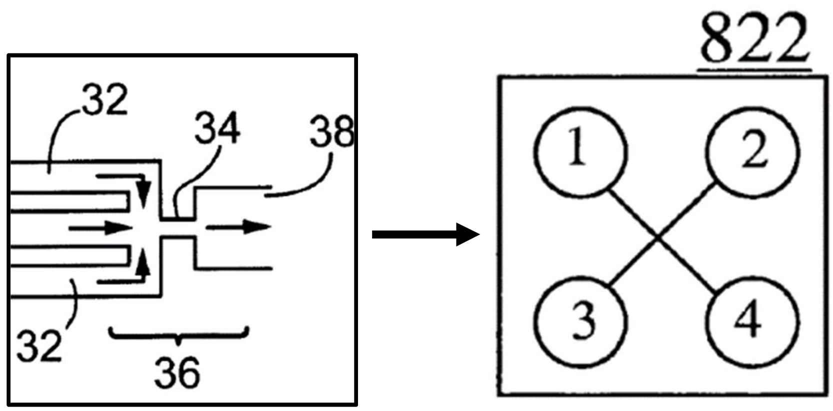


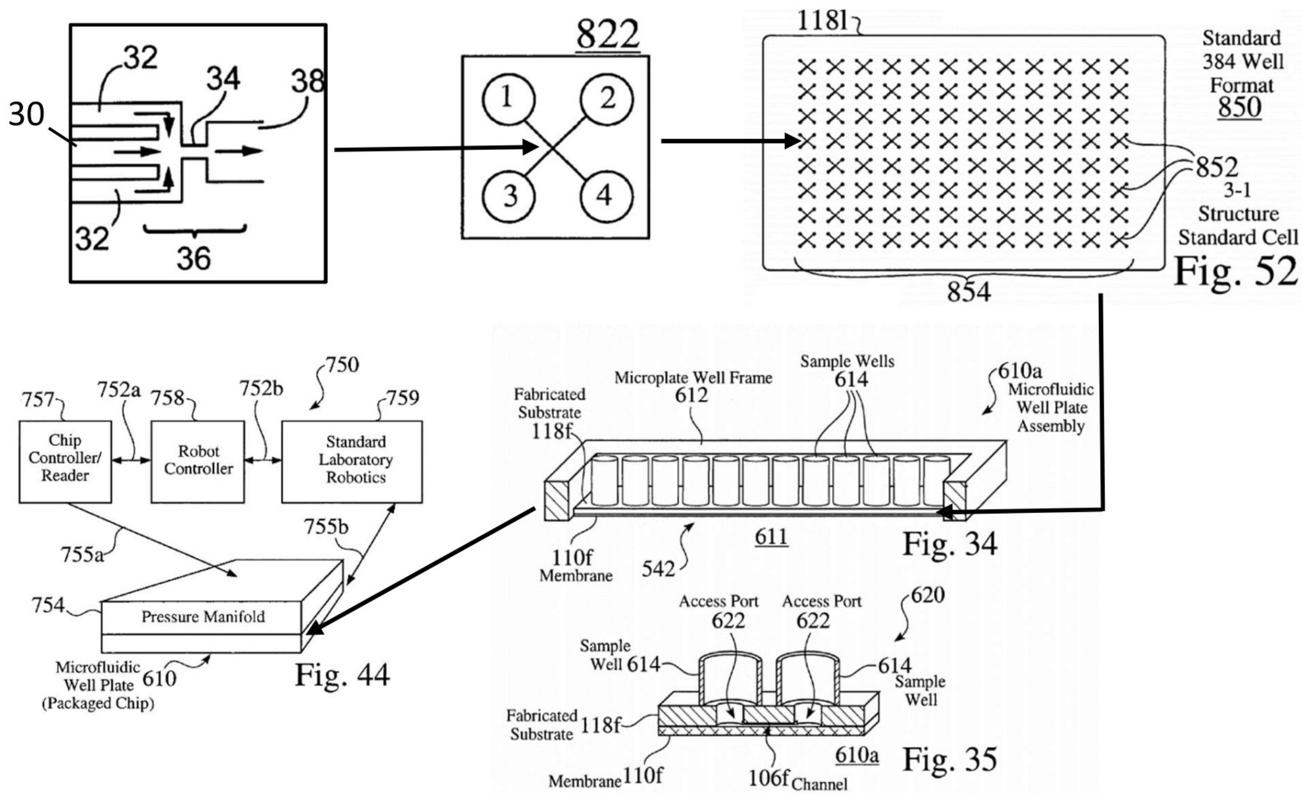
Fig. 50

[4] Hereafter, all emphasis is added unless otherwise indicated.

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 ¶60.) 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 ¶61.) 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*. ¶62) At the time of filing, emulsion or droplet based PCR typically involved analysis of less than 5,000 droplets. (Ex. 1010 ¶94.) Each unit cell of the Combined System would thus hold **25X more droplets than needed for microfluidic PCR**. (Ex. 1003 ¶62.) 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*.) 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 ¶63.)

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 ¶64.) 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.*, 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, 176-77, 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 ¶¶238-40; Ex. 1003 ¶65.) 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 ¶65.)

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 ¶66.) As noted by Kawai, Karnik, Quake and Nisisako, for example, use of parallel emulsion generators substantially increases through put and makes the devices useful in the context of industrial scale synthesis and biochemical analyses. (Ex. 1037 pp. 1-3; Ex. 1030; Ex. 1021 ¶239; Ex. 1031 pp. 1-7; Ex. 1003 ¶66; Ex. 1014 ¶79.) 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 ¶66.) 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.*)

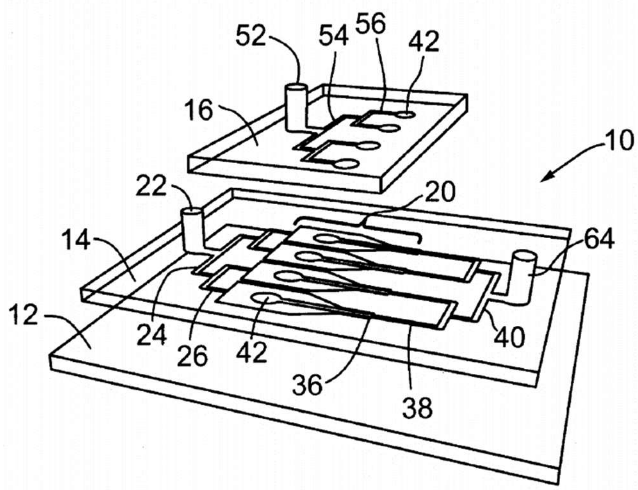
A skilled artisan would have had a reasonable expectation of success in making the Combined System. (Ex. 1003 ¶67.) Modlin explains "[m]anufacturing of the assemblies of the present teachings may be carried out by any number of microfabrication techniques that are well known in the art." (Ex. 1005 ¶160.) 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 '160 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 '160 patent's failure to describe any manufacturing techniques. (Ex. 1003 ¶67.)

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 '160 patent without undue experimentation. (Ex. 1003 ¶¶54-68.)

Preamble

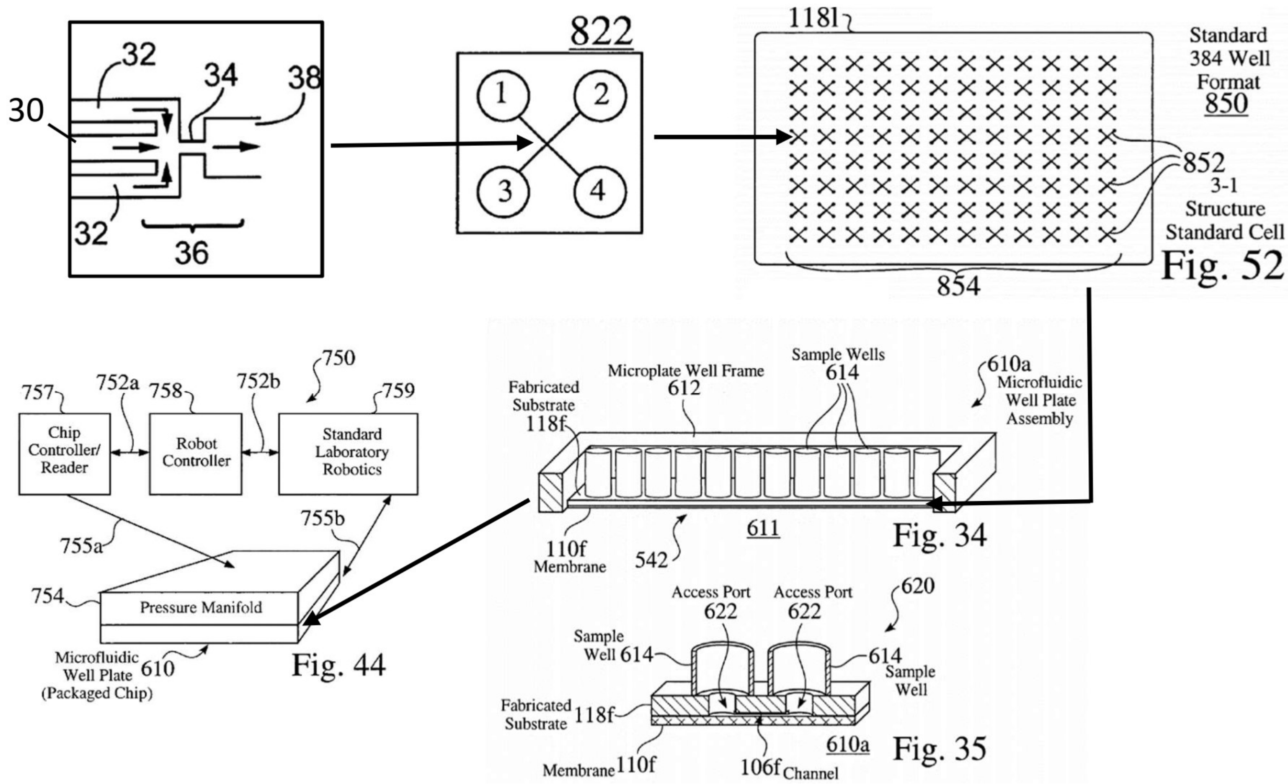
The preamble of claim 1 recites "[a] system for forming an array of emulsions in parallel, comprising."

Assuming arguendo that the preamble is limiting, Kumacheva discloses a system for forming an array of emulsions in parallel. (Ex. 1003 ¶69.) 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 in parallel, meeting the language of the preamble. (Ex. 1003 ¶71.)



***The Combined System also produces an array of emulsions in parallel*.**

(Ex. 1003 ¶¶70-71.) 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 providing 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 ¶¶72-73.) 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 (emphasis added); Ex. 1017 at 16-18.)[5] Kumacheva's patterned sheet 14 thus meets claim 1[a]. (Ex. 1003 ¶73.)

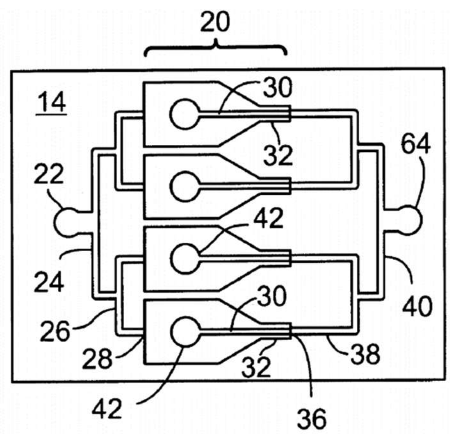
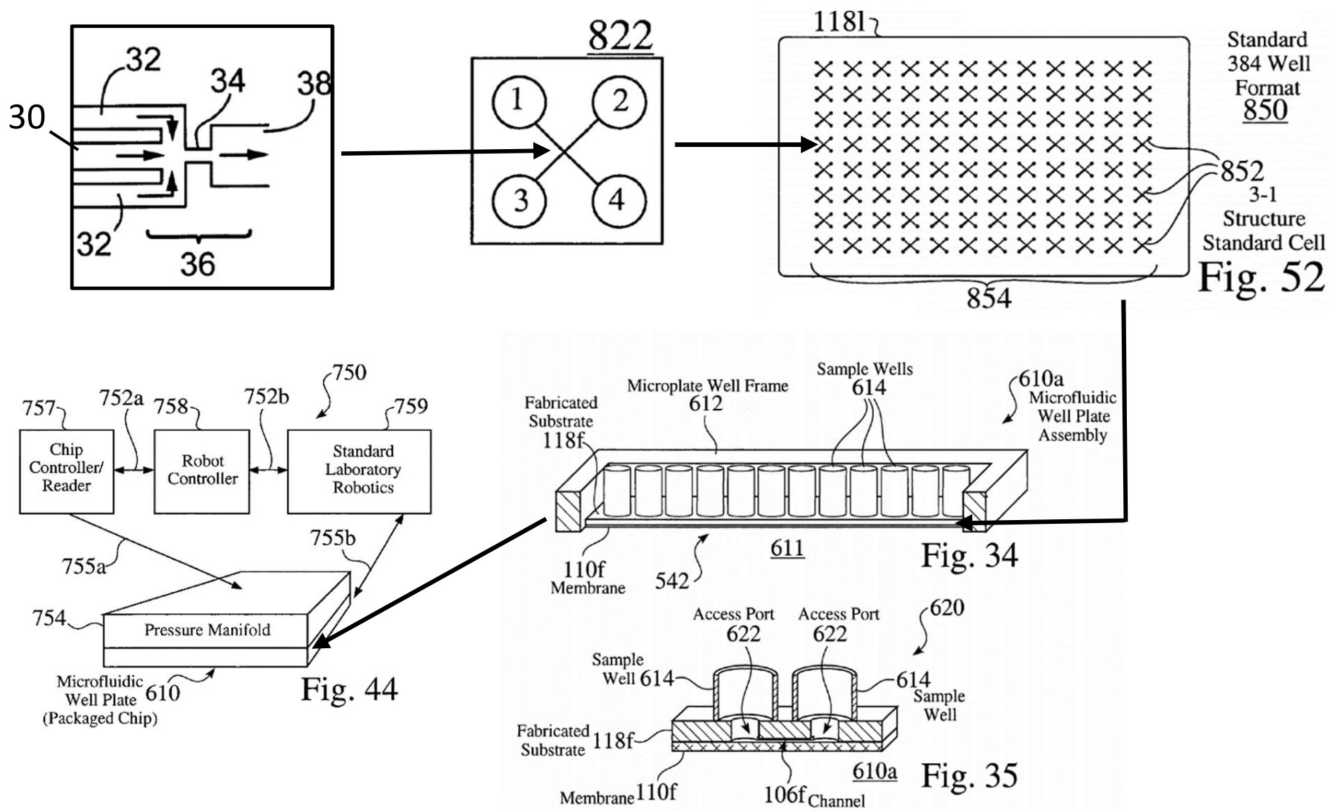


FIG. 4

[5] Hereafter, all emphasis is added unless otherwise indicated.

In the Combined System, the 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 ¶¶74-76.) 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 ¶¶177-78, 201-02, 208-14; Ex. 1003 ¶74.)



Element 1[a][i]

Claim element 1[a][i] recites "each [unit] configured to produce a separate emulsion."

The Combined System includes the recited unit "configured to produce a separate emulsion." (Ex. 1003 ¶¶78-79.) In the Combined System described above, each unit cell has its own output well 2 which receives an emulsion from the droplet generator of that unit cell. (*Id.*) 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 1[a][i]. (*Id.*)

Element 1[a][i] is thus rendered obvious by Kumacheva taken in view of Modlin. (*Id.*)

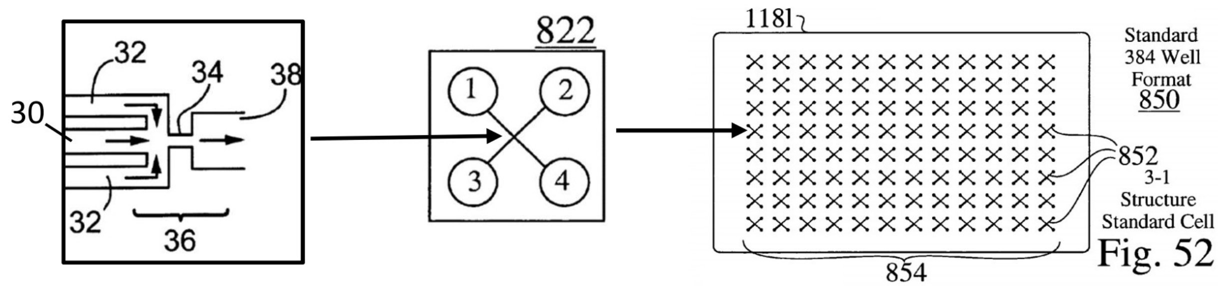
Element 1[a][ii]

Claim element 1[a][ii] recites "a set of wells interconnected by a set of channels forming a channel junction."

The Combined System includes the recited "set of wells interconnected by a set of channels." For example, the Combined System includes input channels that extend from the respective input wells. (Ex. 1003 ¶80.) 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 also includes "an output channel extending from the channel junction to the output well." (*Id.*, *see also* ¶100.) 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 output wells 2 for the water-in-oil emulsion. (Id.)

The flow focusing device 36 of the Combined System is the recited "channel junction." (Ex. 1003 ¶80.) 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 p. 16; see also Ex. 1004 ¶¶31, 37, 70, Ex. 1017 pp. 13, 19, 31; Ex. 1003 ¶80.) In the Combined System the FFD 36 is the recited channel junction. (Ex. 1003 ¶80.)



Accordingly, the Combined System meets element 1[a][ii]. (Ex. 1003 ¶82.)

<u>Element 1[a][iii]</u>

Claim 1[a][iii] recites "each channel of the set of channels being bounded circumferentially."

Kumacheva teaches that the channels are circumferentially bounded. (Ex. 1003 ¶83.) 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 ¶83.)) 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][iii]. (Ex. 1003 ¶83.)

The channels of the Combined System are circumferentially bounded. (Ex. 1003 ¶¶84-85.) In the illustrative example of the combined system shown above, the channel network connecting wells 1 through 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][iii]. (*Id.*)

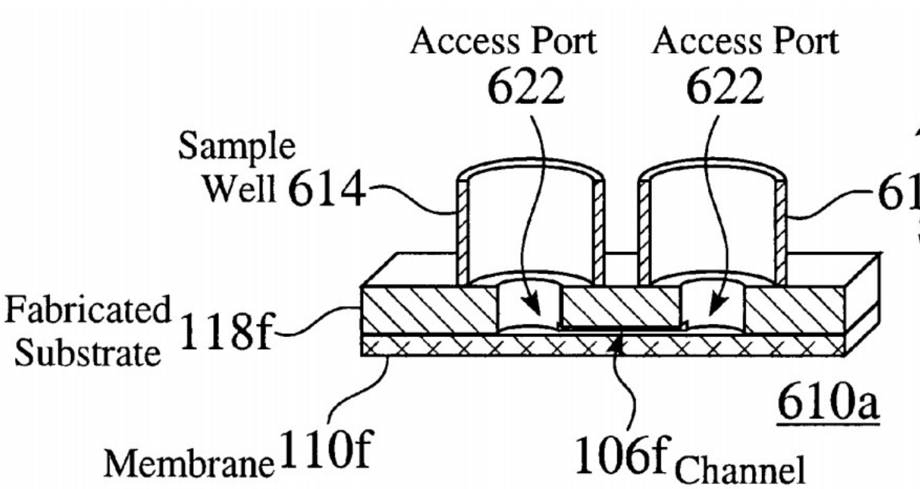


Fig. 35

Moreover, Kumacheva and Modlin render element 1[a][iii] 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 ¶¶85-86.)

Element 1[a][iv]

Claim element 1[a][iv] recites "each set of wells including at least one first input well to receive a continuous phase." The '160 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][iv]. (Ex. 1003 ¶91.)

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 ¶89.) "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.)

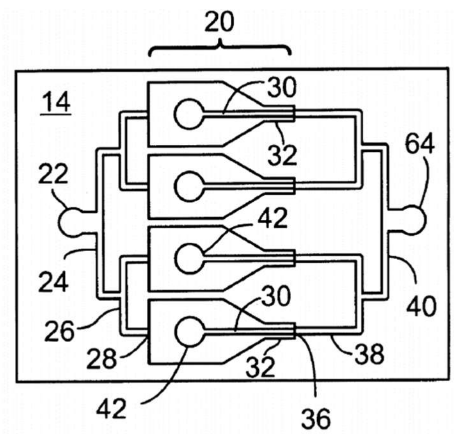
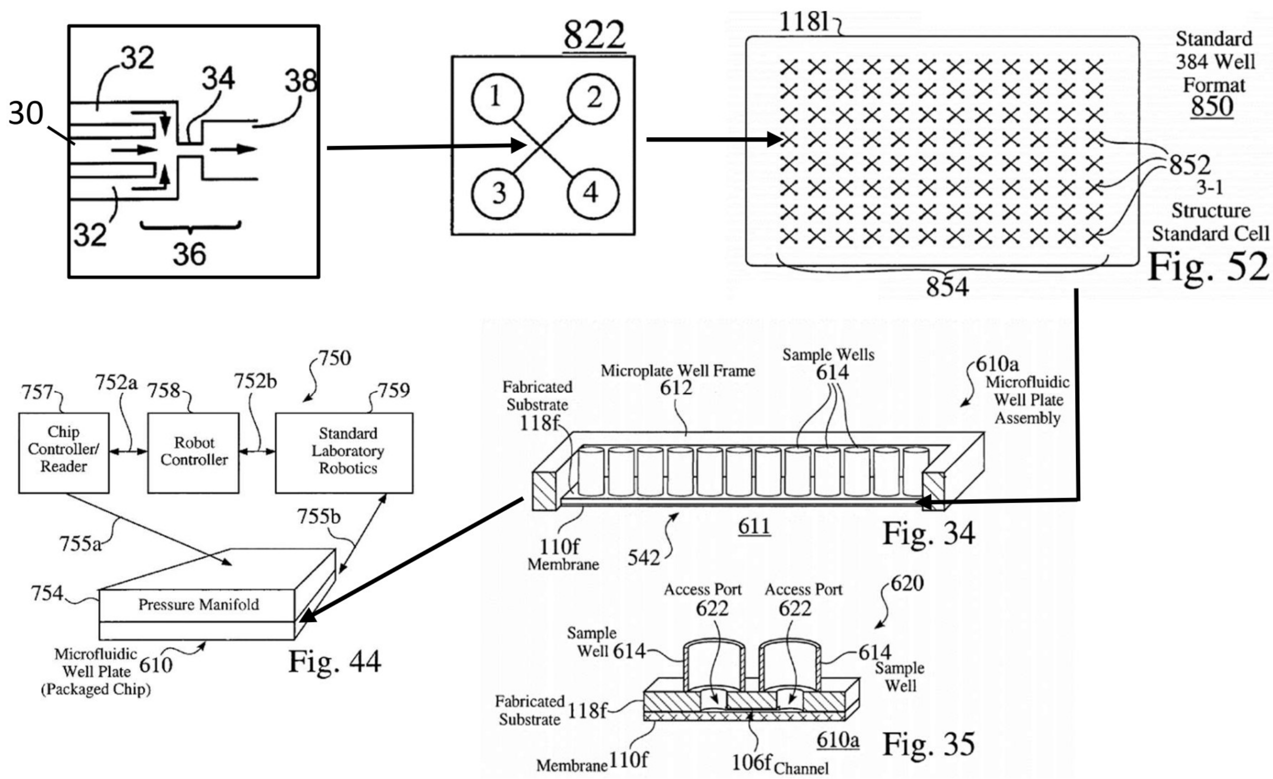


FIG. 4

Modlin teaches that the various unit cells include upwardly extending sample wells 614 as depicted in Fig. 35. (Ex. 1005 ¶¶175-80; Ex. 1003 ¶90.)

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 ¶91.)



The wells 614 above ports 1, 4 meet element 1[a][iv] in the combined system, an example of which is depicted above. (*Id.* ¶¶91-92.)

Element 1[a][v]

Claim element 1[a][v] recites that each emulsion production unit includes "a second input well to receive a dispersed phase." 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][v]. (Ex. 1003 ¶94.)

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 ¶93.) "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 ¶94.)

The dispersion phase well of the Combined System meets element 1[a][v]. (*Id.* ¶¶94-95.)

Element 1[a][vi]

Claim 1[a][vi] recites "an output well." The output well of Combined System meets element 1[a][vi].

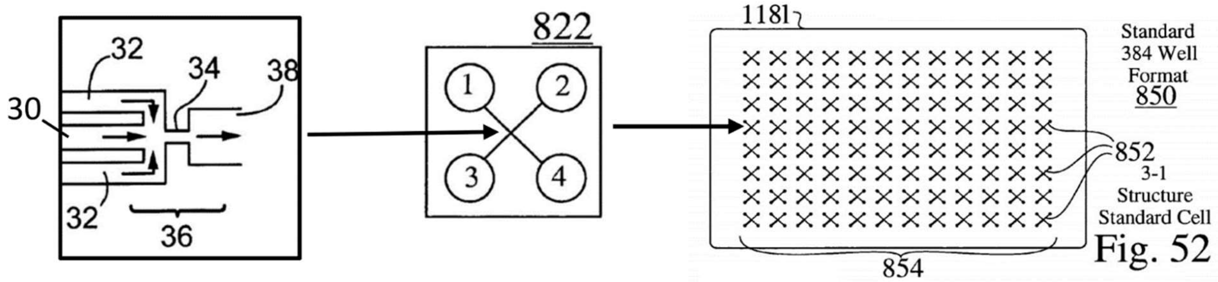
The Combined System includes an output well. Kumacheva teaches that "Liquid A . . . travels downstream via the central microchannel 30 through orifice 34 to the outlet microchannels 38." (Ex. 1004 ¶62; see also Ex. 1017 pp. 13, 16-18.) "Liquid B . . . travels through microchannel 32 through orifice 34 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 output wells 2 for the water-in-oil emulsion. (*Id.*)

The output well of the Combined System thus meets element 1[a][vi]. (Ex. 1003 ¶¶96-97.)

Element 1[b]

Claim 1[b] recites "wherein the set of channels includes at least two input channels extending separately from the input wells to the channel junction, at which droplets of the dispersed phase are generated in the continuous phase, and an output channel extending from the channel junction to the output well, in which an emulsion is collected."

The Combined System includes "at least two input channels extending separately from the input wells to the channel junction." (Ex. 1003 ¶99.) In the example of the 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 flow focusing device 36 of the Combined System is the recited "channel junction." (*Id.* ¶99.) 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 ¶99.) In the Combined System, the FFD 36 is the recited channel junction. (Ex. 1003 ¶99.)

The Combined System includes "an output channel extending from the channel junction to the output well, in which an emulsion is collected." (Ex. 1003 ¶100.) 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 output well 2 which collects the water-in-oil emulsion. (Ex. 1003 ¶100.)

The output well of the Combined System thus meets element 1[b]. (*Id.* ¶¶99-101.)

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

2. Dependent Claim 3

Claim 3 depends from claim 1, and the analysis for claim 1 in Section VIII.A.1 is incorporated by reference.[6] Claim 3 recites that "only one of the channels of each unit extends from the second input well to the channel junction of

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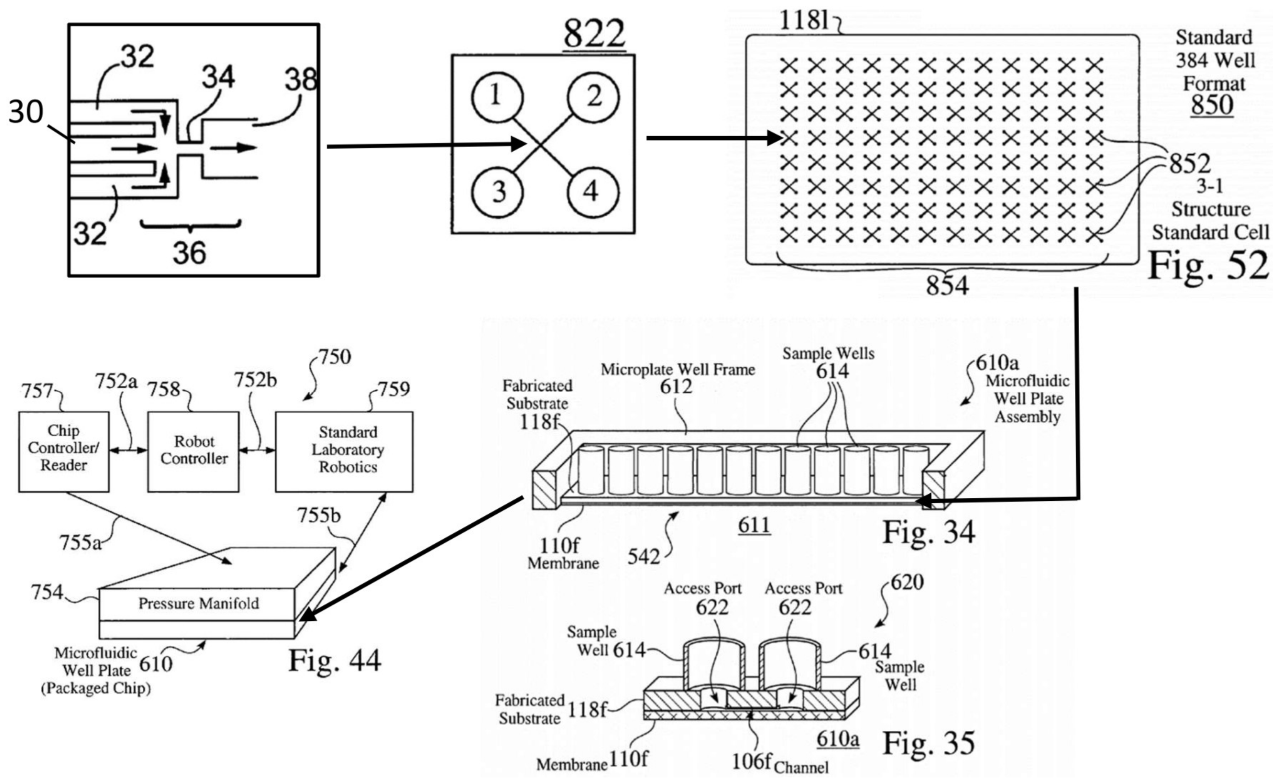
[6] Hereafter, the analysis for the base claim(s) of any dependent claim is incorporated by reference into the analysis for the dependent claim.

such unit, and wherein only one of the channels of each unit extends from the channel junction to the output well of such unit."

The Combined System includes only one channel extending from the second (aqueous phase) input well to the channel junction and only one channel extending from the channel junction to the output well. (Ex. 1003 ¶¶103-05.) In the example Combined System illustrated below, channel 30 extends from the input well above port 3 to the flow focusing device 36 (channel junction). (Id. ¶105.) Channel 38 extends from the follow focusing device 36 to the output well above port 2. (*Id.*)



The channels and wells of the Combined System thus meet Claim 3. (Ex. 1003 ¶¶104-06.)

3. <u>Dependent Claim 4</u>

Claim 4 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 ¶107.) 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 generator10 (QDG) with four parallel flow-focusing devices 20." (Ex. 1004 ¶63; Ex. 1017 p. 16; Ex. 1003 ¶107.) Kumacheva thus meets claim 4.

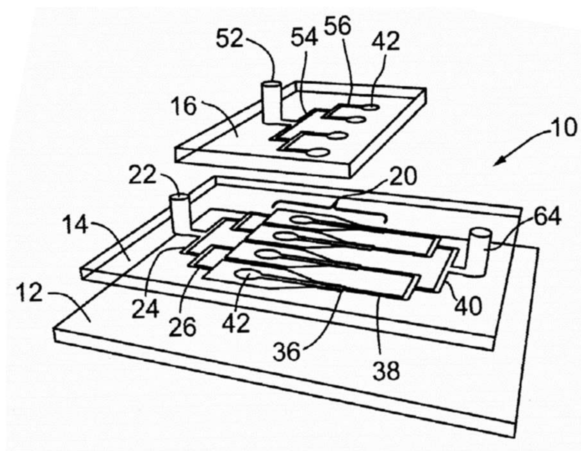


FIG. 3

The Combined System also includes an array of three or more emulsion production units. (Ex. 1003 ¶108.) 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 4.

4. Dependent Claim 5

Claim 5 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 ¶¶111-12.) "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 ¶113.) 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.*) The Combined System thus meets claim 5.

5. Dependent Claims 6-7

Claim 6 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 7 depends from claim 6 and 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 6-7. (Ex. 1003 ¶¶116, 120.) "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 38." (Ex. 1004 ¶62; Ex. 1017 pp. 16-19.)

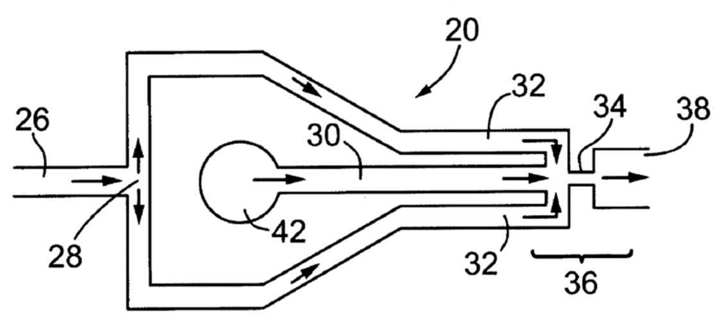
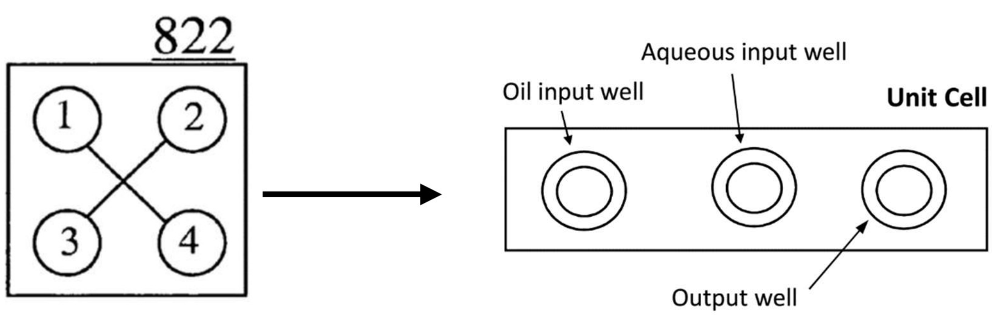


FIG. 2

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 ¶¶116, 120.)

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 ¶¶117, 121.) This modification of the Combined System is illustrated below. (*Id.* ¶118.) The 4-well unit cell 822 in the Combined System is replaced with a 3-well unit cell. (*Id.*) Although not required by claims 6-7, this arrangement is consistent with using a plate having wells positioned at industry standard spacing. (*Id.*)



A skilled artisan would have seen various reasons to make this modification. (*Id.* ¶¶117, 132.) 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*. at ¶¶225-234.) Regarding the Combined System, one 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 ¶¶116-117, 120-121.) 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, one 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 claims 6 and 7. (*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 6 and 7. (Ex. 1003 ¶¶119, 122.)

6. Dependent Claim 8

Claim 8 depends from claim 1 and recites that "each channel of each unit extends to the channel junction of such unit from a bottom region of a 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 ¶¶175-80; Ex. 1003 ¶124.)

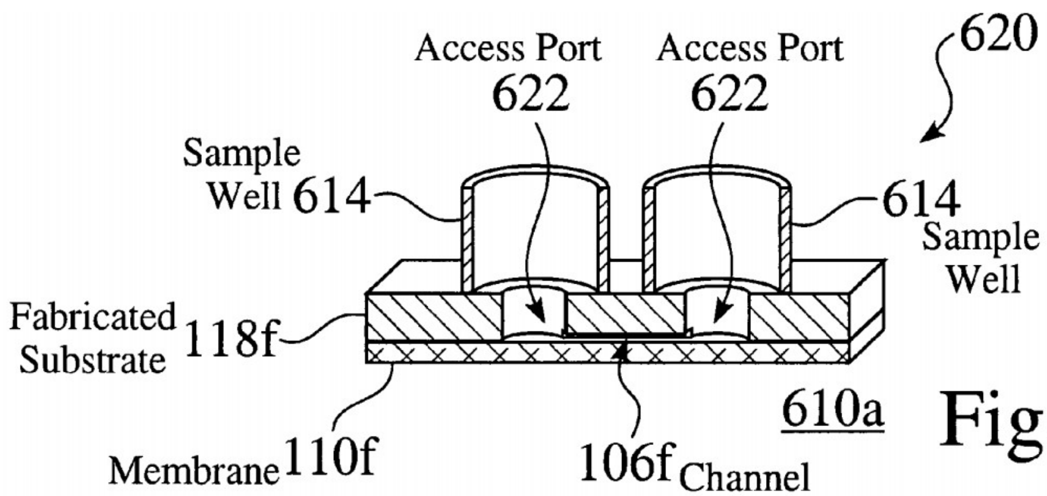


Fig. 35

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 ¶124.) 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 ¶¶208-14; Ex. 1003 ¶124.) The unit cells have the structure shown in Fig. 35, reproduced above. (Ex. 1003 ¶124.)

7. Dependent Claim 9

Claim 9 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 the channels of each unit, and wherein the lower member extends under each well and channel of each 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 9. Modlin teaches that the

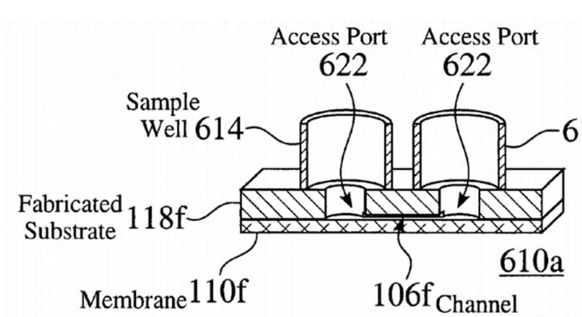


Fig. 35

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 ¶¶175-80; Ex. 1003 ¶128.) 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 ¶128.)

In the combined system of Kumacheva and Modlin, this channel/well configuration is preserved, thus meeting the recitations of claim 9. (*Id.*) This aspect of the Combined System is discussed above in connection with claim 1.

8. <u>Dependent Claim 10</u>

Claims 10 depends from claim 9 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 9, Modlin teaches that the plate includes an upper member (substrate 118 including wells 614). (Ex. 1003 ¶131.)

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 ¶131.) Injection molding was well-known to be an economical process, and it was well-recognized 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 ¶131.) 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 ¶131.) 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." (Ex. 1041p. 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 ¶131.) As of September 2008, skilled artisans understood that microfluidic chips could 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. 23-35; Ex. 1041 p. 12; Ex. 1006 p. 2; Ex. 1003 ¶131.) 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 ¶131.) Such would require no more than routine skill and would lead to predictable results. (*Id*.)

Claim 10 is thus rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶132.)

9. <u>Dependent Claim 11</u>

Claims 11 depends from claim 9 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 ¶133.) 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 ¶¶155-74; Ex. 1003 ¶133.) The lower member of the Combined System has this same structure and thus meets claim 15. (Ex. 1003 ¶¶133-34.)

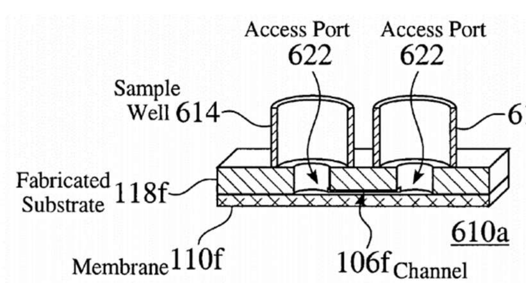
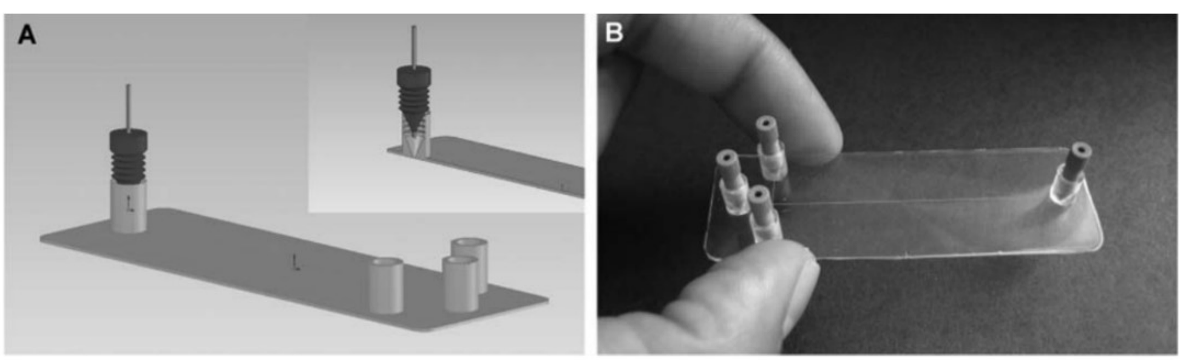


Fig. 35

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 ¶133.) Doing so would substantially simplify the manufacturing process and reduce cost. (*Id.*) Other advantages of injection molding are discussed above in connection with claim 10.

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 ¶134.) 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 ¶134.) 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 11. (Ex. 1003 ¶135.)

10. Dependent Claim 12

Claim 12 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 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 under 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 ¶137.) 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 ¶¶175-80; Ex. 1003 ¶137.)

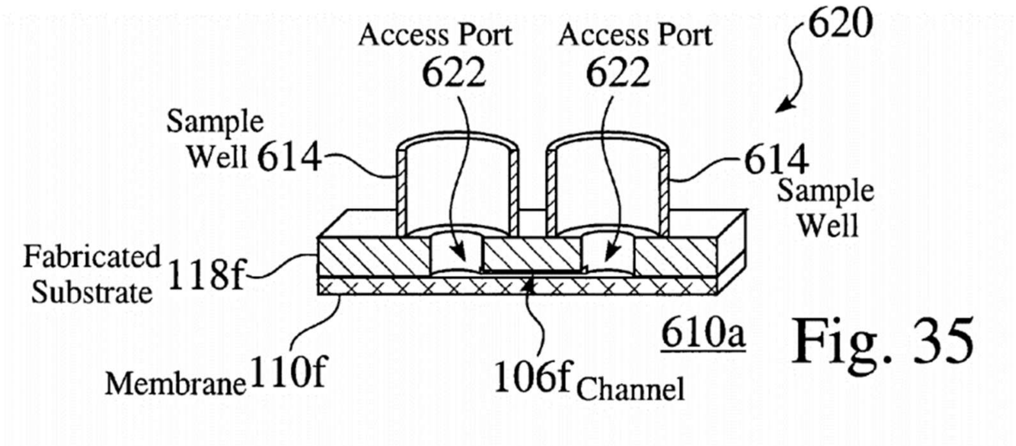


Fig. 35

Modlin teaches a lower member (membrane 110) having a surface that forms a bottom wall below each through-hole and groove. (Ex. 1003 ¶137.) As illustrated in Fig. 35, above, membrane 110 (lower member) forms the bottom of the channels 106 and extends below the through holes 622, as depicted in Fig. 35 reproduced below. (Ex. 1005 ¶¶175-80; Ex. 1003 ¶137.)

In the Combined System, the unit cells have this same structure, thus meeting the recitations of claim 12. (Ex. 1003 ¶138.)

11. Dependent Claim 13

Claim 13 recites that "the lower member is a sheet of material that is substantially thinner than the upper member." The '160 does not define what "substantially thinner" means; rather, the '160 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 88:57-64.)

***Modlin's membrane 110 is substantially thinner than the upper member (substrate 118 and wells 614), thus meeting the recitations of claim 13*.** 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 ¶¶175-80; Ex. 1003 ¶139.) 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 ¶139.) 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 13. (*Id.*)

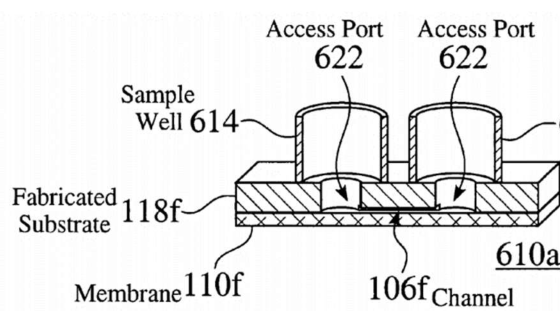


Fig. 35

In the Combined System, the unit cells have this same structure, thus meeting the recitations of claim 13. (Ex. 1003 ¶¶141-42.)

12. Dependent Claim 15

Claim 15 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."

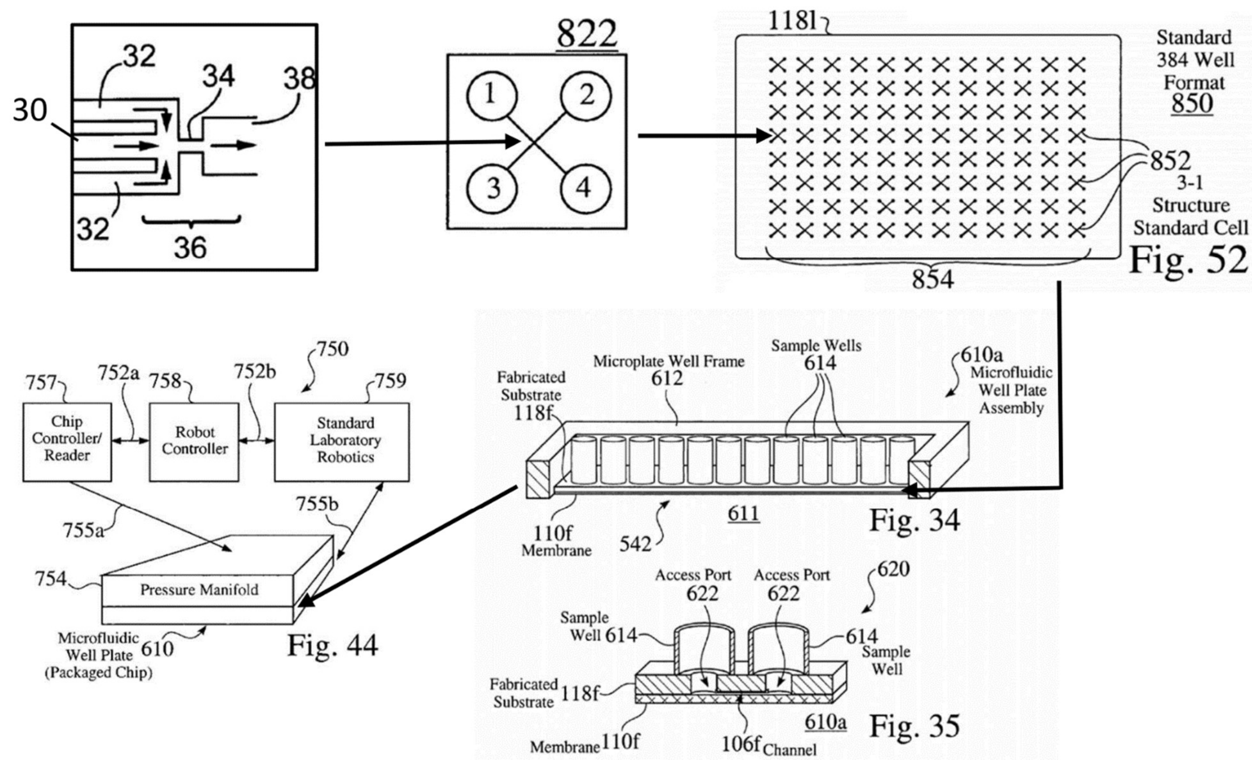
In the Combined System described in connection with claim 1, each unit cell includes an emulsion generator and each has an input well that is not shared with other emulsion generators in other unit cells. (Ex. 1003 ¶¶143-45.) The Combined System thus meets claim 15. (*Id*.)

13. Dependent Claim 16

Claim 16 depends from claim 1 and recites "an instrument configured to create a pressure drop between the input wells and the output well of each unit such that the continuous phase and the dispersed phase of each unit are driven from the input wells, through the channel junction, and to the output well of such unit, for collection as an emulsion including droplets of the dispersed phase disposed in the continuous phase."

The Combined System includes the recited instrument configured to create a pressure drop between the input wells and output well as recited in claim 16. (Ex. 1003 ¶¶146-49.) 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.)

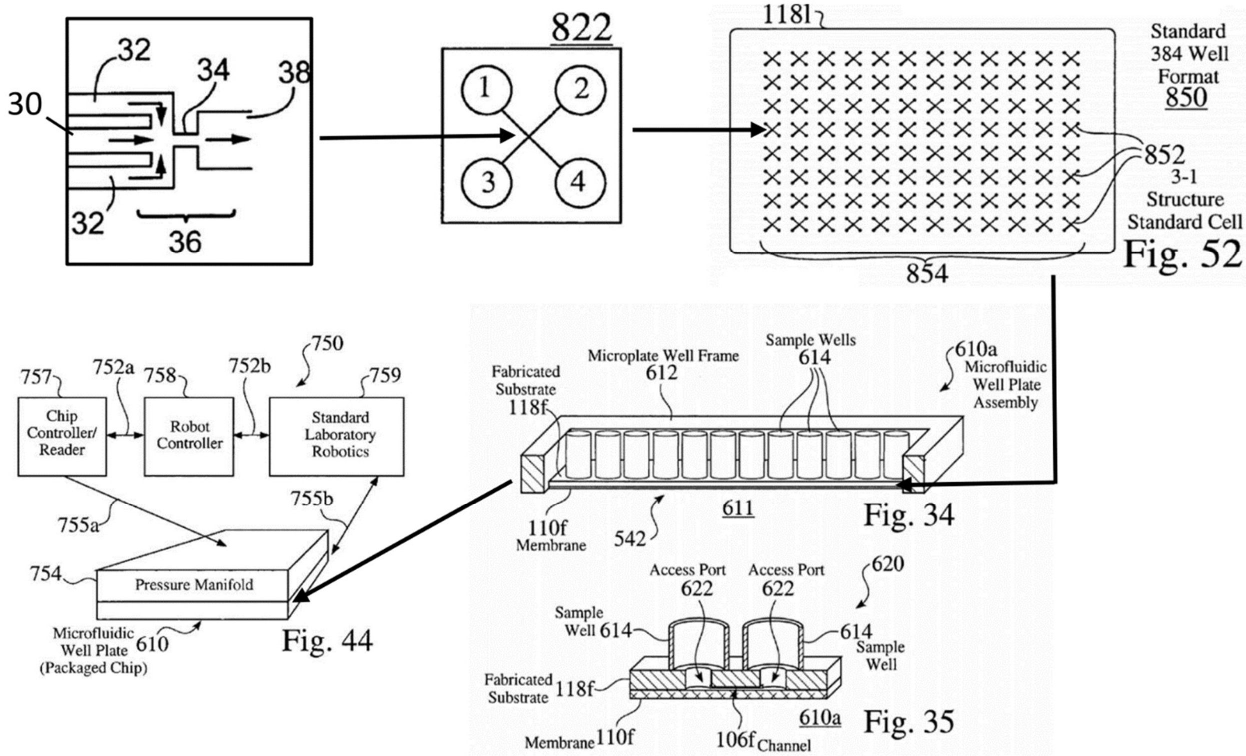


In the exemplary combined system depicted above, pressure is applied at input wells 614 above access ports 1, 3 and 4, to drive the emulsion to the output well above port 2. (Ex. 1003 ¶149.) As noted above, as the fluids pass through the channels and junction, the pressure drops by virtue of the resistance to flow created by the channels and the constriction. (Ex. 1033 pp. 1-4; Ex. 1007 pp. 2-3; Ex. 1003 ¶149.)

14. <u>Dependent Claim 18</u>

Claim 18 depends from claim 16 and recites that "the instrument includes a pressure source."

The Combined System includes the recited pressure source. (Ex. 1003 ¶¶151-53.) 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.)



The Combined System thus meets claim 18. (Ex. 1005 ¶¶186-90, 219-225; Ex. 1003 ¶154.)

15. Independent Claim 20

Claim 20 is the same as claim 1 except for the additional limitations of "a plate having an upper member attached to a lower member" 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."

The discussion of the claim elements of claim 1 is incorporated by reference.

The additional features recited in claim 20 are duplicative to those recited in claims 9 and 12. The discussion of claims 9 and 12 is incorporated by reference.

16. Dependent Claim 21

Claim 21 depends from claim 20 and recites that "each of the upper and lower members is formed by a respective, continuous piece of material."

The discussion of claim 11 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. (Ex. 1003 ¶¶158-59.)

For the foregoing reasons claims 1, 3-13, 15-16, 18 and 20-21 are rendered obvious by Kumacheva taken in view of Modlin. (Ex. 1003 ¶160.)

B. Ground 2: Claims 17 and 19 Are Rendered Obvious by Kumacheva in View of Modlin and Further in View of Chien

1. Dependent Claim 17

Claim 17 depends from claim 16 and recites that "the instrument includes a vacuum source."

In the Combined System discussed above in connection with claim 1, the microfluidic well plate assembly 610 has an array of FFD-containing unit cells and is placed in contact with Modlin's pressure manifold 754. The manifold 754 provides either positive or negative pneumatic (air) pressure to drive the fluids among the

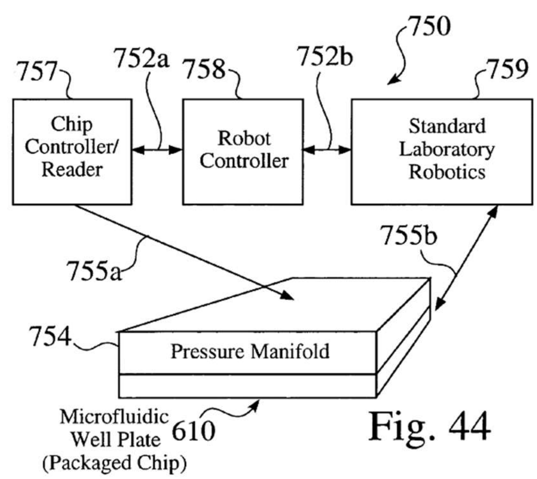


Fig. 44

microwells 1-4 in each unit cell 822. (Ex. 1005 ¶¶187-88, 202, 225; Ex. 1003 ¶162.) However, because Modlin's discussion of the pneumatic control is abbreviated, Petitioner relies upon Chien for its teaching of using air pressure (positive pressure or vacuum) in the wells to drive the fluids. (Ex. 1003 ¶163.)

Chien teaches that it is preferable to drive fluids through microfluidic chips with a manifold that delivers air pressure (vacuum or positive 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.*) 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.)

A skilled artisan would have been strongly motivated to use Chien's vacuum/pressure drive to improve upon the combined Kumacheva/Modlin device. (*Id.*; Ex. 1003 ¶164.) Modlin expressly suggests use of air pressure to drive the fluids in the wells by teaching that instrument 740/750 provides "pneumatic or hydraulic" pressure. (Ex. 1005 ¶152-53, 187-88, 192, 202, 332, claim 12.) 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 ¶164.) A skilled artisan would be motivated to use the Chien technique to drive fluids in the Combined System because, as noted by Chien, using this technique enables more precise and reproducible control of the fluid flows. (Ex. 1007 pp. 1-3; Ex. 1003 ¶164.)

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 ¶¶164-65.)

2. Dependent Claim 19

Claim 19 depends directly from claim 16 and recites that "the instrument is configured to operate the emulsion production units without contacting liquid contents of any wells of the units."

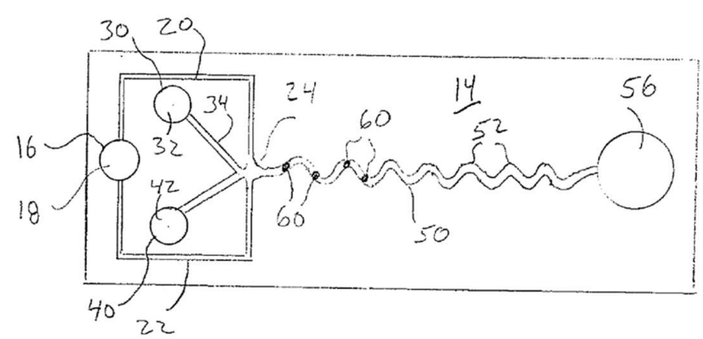
The discussion of claim 17 is incorporated by reference. As discussed therein the Combined System as modified by Chien uses air pressure to drive the liquid in each well such that the liquid is not contacted by the instrument or another liquid. (Ex. 1003 ¶167.) The instrument 740/750 of the Combined System thus meets claim 19.

For the foregoing reasons claims 17 and 19 are rendered obvious by Kumacheva taken in view of Modlin and further in view of Chien. (Ex. 1003 ¶¶161-69.)

C. Ground 3: Claim 2 Is Rendered Obvious by Kumacheva in View of Modlin and Further in View of Hsieh

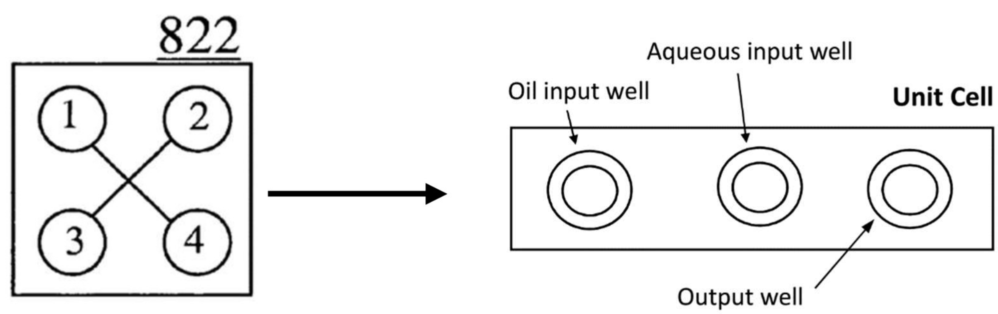
Claim 2 depends from claim 1 and recites that the "set of wells of each unit includes only one first input well, and wherein a pair of channels of the set of channels of each unit extend separately from one another to the channel junction of such unit from the only one first input well."

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. 1018 ¶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. (Ex. 1003 at ¶172.)

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. (*Id.* ¶173.) 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 6-7, 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, one skilled in the art would use a single continuous phase well (first input well) as recited in claim 7. (*Id.*)

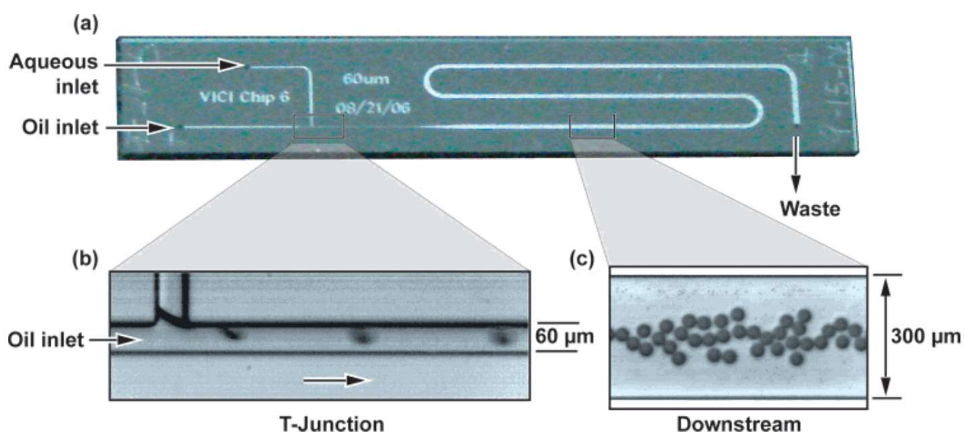
A skilled artisan would thus have considered it obvious to use a single input well to improve a similar system (the Combined System of Kumacheva and Modlin) in the same way (to simplify the instrument and save space on the chip). *KSR*, 550 U.S. at 415-421 (2007) (*Id.*)

In light of the level of skill of art described in Section V, which is incorporated by reference, a skilled artisan would have found it routine to make the foregoing combination (yielding the claimed limitation). (Ex. 1003 ¶174.)

D. Ground 4: Claim 14 Is Rendered Obvious by Kumacheva in View of Modlin and Further in View of Beer

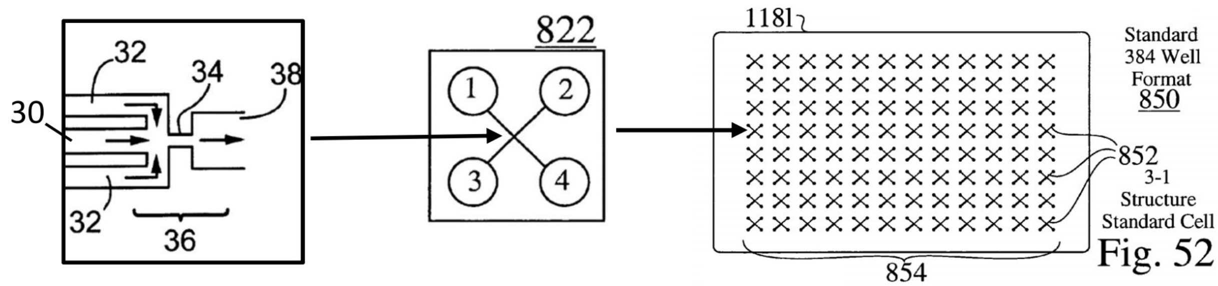
Claim 14 depends from claim 1 and recites that "the first input well of a unit contains a nonaqueous continuous phase, wherein the second input well of such unit contains an aqueous phase configured for PCR amplification, and wherein the output well of such unit contains an emulsion including droplets of the aqueous phase disposed in the nonaqueous continuous phase."

Beer teaches performing PCR in droplets formed with microfluidic emulstion 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 14. (Ex. 1003 ¶¶175-76.) 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 14. (*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 14. (Ex. 1003 ¶177.) 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." (*Id.*) 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) (Ex. 1003 ¶178.)

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 ¶¶178-79.)

Thus Claim 14 is rendered obvious by Kumacheva and Modlin taken further in view of Beer. (Ex. 1003 ¶¶175-79.)

E. Ground 5: Claims 8-13 and 20-21 Are Rendered Obvious by Kumacheva in view of Modlin and Further in view of Soane

Claims 8-13 and 20-21, 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 at 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*. at Abstract.) Shown in Fig. 6 (right) is "an assembled microchannel

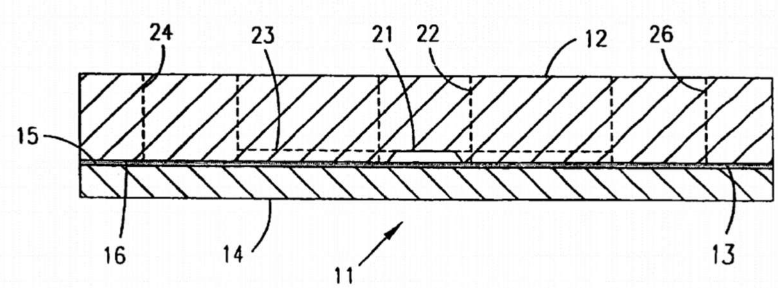


FIG. 6

device 10 made 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*. at 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 ¶182.)

One skilled in the art would have had a reasonable expectation of success using the Soane method to fabricate the Combined System. (Ex. 1003 ¶183.) 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. <u>Dependent Claim 8</u>

The text of claim 8 is reproduced in Section VIII.A.6.

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 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 ¶¶184-86.)

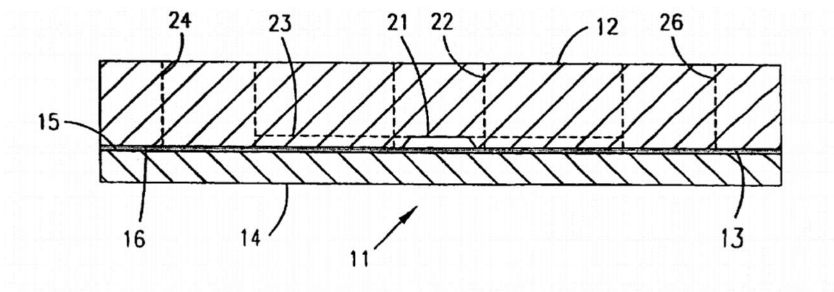


FIG. 6

2. Dependent Claim 9

The text of claim 9 is reproduced in Section VIII.A.7.

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.

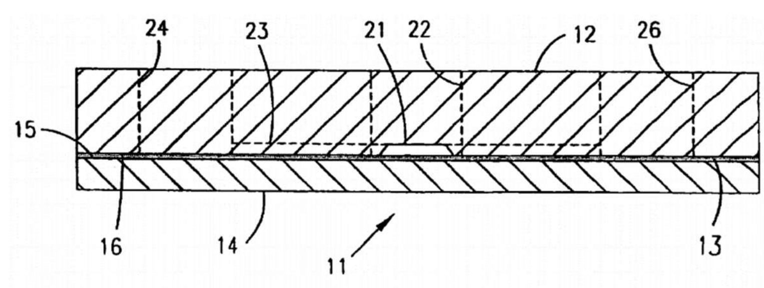


FIG. 6

1003 ¶¶187-88.) “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 at 5:55-64, see also Examples 1-8 at 9:65-13:7.) The Soane structure thus meets claim 9. (Ex. 1003 ¶¶187-88.)

3. Dependent Claim 10

The text of claim 10 is reproduced in Section VIII.A.8.

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 10. (Ex. 1003 ¶¶189-90.)

4. Dependent Claim 11

The text of claim 10 is reproduced in Section VIII.A.9.

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. 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 ¶191.) "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 11. (Ex. 1003 ¶¶191-92.)

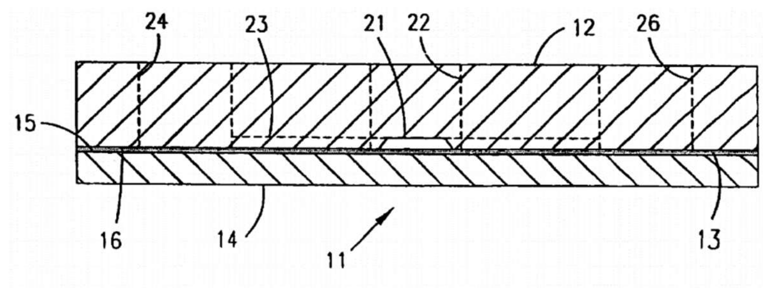


FIG. 6

5. Dependent Claim 12

The text of claim 12 is reproduced in Section VIII.A.10.

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 and groove. (Ex. 1028 at 5:45-64, *see also* Examples 1-8 at 9:65-13:7; Ex. 1003 ¶193.) The base plate 12 and bonding material film 16 of Soane thus meet claim 12. (Ex. 1003 ¶¶193-95.)

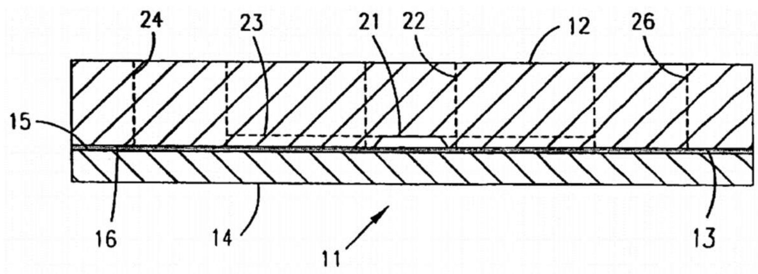


FIG. 6

6. Dependent Claim 13

The text of claim 13 is reproduced in Section VIII.A.11.

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 Figs. 5 and 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 ¶196.)

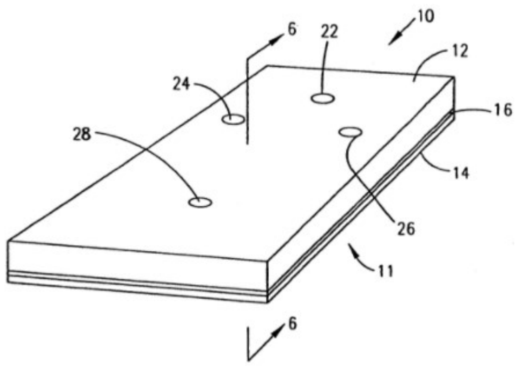


FIG. 5

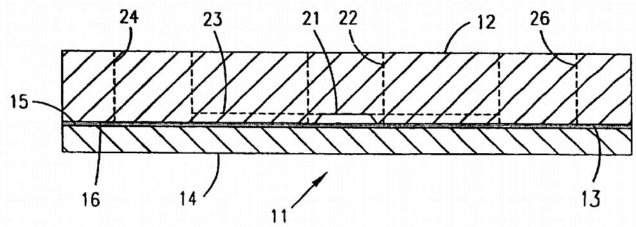


FIG. 6

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 1µm whereas the base plate 12 is usually on the order of at least 50 µm. (Ex. 1003 at ¶196.)

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 um) or greater.

Under either approach, Soane thus meets the recitations of claim 13.

7. Independent Claim 20

Claim 20 is the same as claim 1 except for the additional limitations of "a plate having an upper member attached to a lower member" 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." The discussion of the claim elements of claim 1 is incorporated by reference.

Additionally, claim 20 recites features duplicative to those recited in claims 9 and 12. The discussion of claims 9 and 12 is incorporated by reference.

8. Dependent Claim 21

Claim 21 depends from claim 20 and recites that "each of the upper and lower members is formed by a respective, continuous piece of material."

The discussion of claim 11 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 8-13 and 20-21 are rendered obvious by Kumacheva and Modlin taken further in view of Soane. (Ex. 1003 ¶¶180-201.)

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 '160 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 '160 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: January 9, 2018

/Greg H. Gardella/

Greg H. Gardella, Reg. No. 46,045
Gardella Grace P.A.
455 Massachusetts Ave. NW, Suite 507
Washington, DC 20001
Tel: (703) 740-4540

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 13,461 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.

Respectfully submitted,

Date: January 9, 2018

/Greg H. Gardella/

Greg H. Gardella, Reg. No. 46,045
Gardella Grace P.A.
455 Massachusetts Ave. NW, Suite 507
Washington, DC 20001
Tel: (703) 740-4540

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 '160 patent to:

Kolisch Hartwell, P.C.
200 Pacific Building
520 SW Yamhill Street
Portland OR 97204

Dated: January 9, 2018

/Greg H. Gardella/
Greg H. Gardella
Reg. No. 46,045