

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BERKELEY LIGHTS, INC.,
Petitioner,

v.

THE UNIVERSITY OF BRITISH COLUMBIA,
Patent Owner.

IPR2021-01249
Patent 10,087,408 B2

Before KRISTINAM. KALAN, CHRISTOPHER M. KAISER, and
CHRISTOPHER L. OGDEN, *Administrative Patent Judges*.

OGDEN, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

Berkeley Lights, Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”) for *inter partes* review of claims 1, 6, 11, 16, 19, 24, 26, 27, and 30 of U.S. Patent No. 10,087,408 B2 (Ex. 1001, “the ’408 patent”). The University of British Columbia (“Patent Owner”) filed a Patent Owner Response (Paper 18, “PO Resp.”), Petitioner filed a Reply to the Patent Owner Response (Paper 22, “Pet. Reply”), and Patent Owner filed a Sur-reply (Paper 29, “PO Sur-reply”).

We held an oral hearing on November 4, 2022, and the transcript is entered on the record. Paper 37 (“Tr.”).

This is a final written decision under 35 U.S.C. § 318(a) as to whether the claims challenged in the *inter partes* review are unpatentable. For the reasons below, we conclude that Petitioner has not shown that any claims of the ’408 patent are unpatentable.

II. BACKGROUND

A. RELATED PROCEEDINGS

As related matters, the parties identify the following three pending U.S. district court cases: *AbCellera Biologics, Inc. v. Berkeley Lights, Inc.*, No. 5:20-cv-08627 (N.D. Cal. filed July 9, 2020); *AbCellera Biologics, Inc. v. Berkeley Lights, Inc.*, No. 5:20-cv-08626 (N.D. Cal. filed Aug. 25, 2020); *AbCellera Biologics, Inc. v. Berkeley Lights, Inc.*, No. 5:20-cv-08624 (N.D. Cal. filed Sept. 16, 2020) (collectively, “parallel district court proceedings”). Pet. 3–4; Paper 6, 1. The District Court has stayed these proceedings

pending the outcome of this and two other *inter partes* review proceedings. See Ex. 1035.

We note that *inter partes* reviews IPR2021-01250 (institution denied on January 21, 2022) and IPR2021-01386 (institution denied on February 1, 2022) also involved the same parties and related technology.

B. THE '408 PATENT (EX. 1001)

The '408 patent issued from an application filed July 7, 2011, claiming priority from U.S. Provisional Application No. 61/362,213, filed July 7, 2010. Ex. 1001, codes (22), (60). It describes methods, in the context of microfluidic devices, “for perfusing a cell with perfusion fluid,” so that “the gravitational forces acting on the cell to keep the cell at or near . . . a retaining position exceed the hydrodynamic forces acting on the cell to move it toward an outlet.” *Id.* at code (57).

Figure 1 of the '408 patent, reproduced below, is a top view of the microfluidic device, with two expanded views at medium resolution (top left, with a 1 mm size reference bar) and high resolution (top right, with a 100 μm size reference bar). Ex. 1001, 6:17–21.

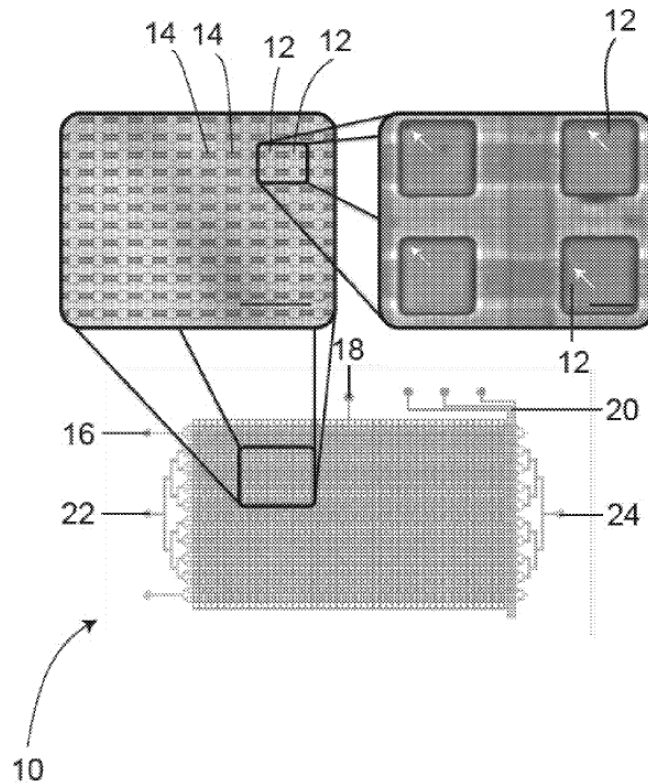
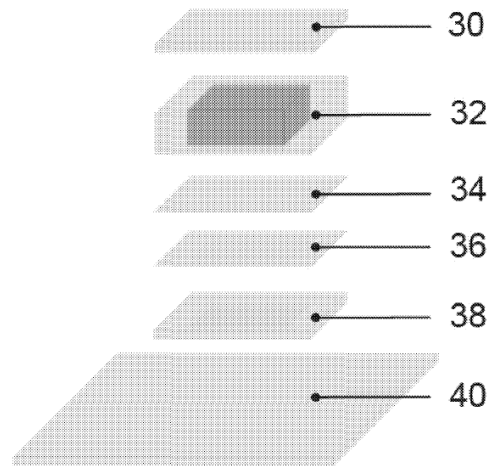


FIGURE 1

Device 10, as depicted in Figure 1 above, comprises an array of 1,600 chambers 12, each “with integrated microvalves to allow precise control and exchange of media.” Ex. 1001, 23:12–13. Fluid enters chambers 12 from array inlet 22 via flow channels 14, and fluid exits through array outlet 24. *Id.* at 23:13–14, 23:18–21. To control cell loading and perfusion rates, device 10 also includes control lines 18 (connected to an isolation valve) and 20 (connected to a peristaltic pump). *Id.* at 23:16–18. Hydration lines 16 are located on each side of the array to minimize edge effects. *Id.* at 23:14–15. In the high-resolution view (shown in top right of Figure 1), arrows point to the location of single cells in each chamber 12. *Id.* at 23:21–22.

Figure 2, reproduced below, is an exploded view of device 10 showing the layers of the device as they are assembled during fabrication. Ex. 1001, 6:22–24, 23:44–46.



As shown above in Figure 2, device 10 includes the following layers (from bottom to top): glass slide 40; chamber layer 38, which includes chambers 12 (not shown); control layer 36, which includes control structures; a 150 μm -thick PDMS¹ membrane 34; iso-osmotic bath layer 32 consisting of a large chamber “filled with medium to prevent evaporation and maintain constant osmolarity inside the chambers [12]”; and “gas-permeable PDMS cover layer 30 to keep the [iso-osmotic] bath sterile.” Ex. 1001, 23:46–63.

Figure 4 of the ’408 patent, reproduced below, is a cross-sectional view of chamber 12 and channel 14 of microfluidic device 10 while chamber 12 is being perfused with a fluid. Ex. 1001, 6:28–32.

¹ According to the ’408 patent, PDMS is an abbreviation for polydimethylsiloxane, “a transparent and biocompatible silicone elastomer . . . widely used for cell-culture applications,” which “provide[s] high gas permeability for the efficient exchange of oxygen and carbon dioxide.” Ex. 1001, 2:38–42.

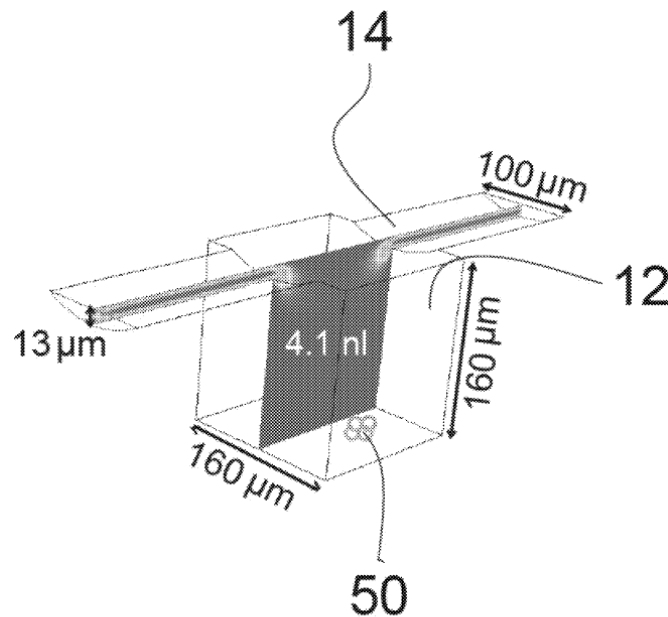


FIGURE 4

Figure 4, above, depicts culture chamber 12 (a cube of 160 μm on each side, forming a volume of about 4.1 nl) and flow channel 14 (100 μm wide and up to 13 μm deep). Ex. 1001, 24:39–40, 24:64–65, 26:20–22. Chamber 12 includes trapped cells 50. *Id.* at 24:36. The '408 patent discusses a numerical simulation that predicts a “sudden expansion when the fluid moves from the flow channel [14] to the chamber [12 that] creates a velocity drop,” and “minimal flow rates at the bottom 5/6 of the chamber.” *Id.* at 26:12–15, 26:23–24. “[T]he gravitational forces on the cells [are] greater than hydrodynamic forces and cells remain in the cell retaining region while the perfusion fluid exits the chamber through the flow channel outlet.” *Id.* at 26:24–28.

After culturing cells 50 in chambers 12, the user can recover them “by simply inverting the device, causing the cells to settle into the higher-flow rate regions of the chambers (as shown in FIG. 4) and then recovering the pooled population by flushing back through the input port.” Ex. 1001,

26:50–53. Alternatively, “when selective recovery of the contents of specific individual wells is desired, the layer of PDMS [30 as shown in Fig. 2] covering the osmotic bath [32] can first be removed and a sterile micropipette then used to pierce the membrane [34] over any selected chamber followed by aspiration of its contents.” *Id.* at 26:57–62.

C. CHALLENGED CLAIMS AND GROUNDS

Claim 1, representative of the challenged claims, reads as follows:

1. A method of culturing a cell, the method comprising:
 - [A] retaining the cell at a retaining position within an individual chamber of a microfabricated device;
 - [B] perfusing the cell with a perfusion fluid by flowing the perfusion fluid into the individual chamber through an inlet and out of the chamber through an outlet,
 - [C] wherein the outlet is positioned such that gravitational forces acting on the cell to keep it at or near the retaining position exceed hydrodynamic forces acting on the cell to move it toward the outlet;
 - [D] culturing the cell within the chamber and monitoring a response in the chamber; and
 - [E] selectively recovering the cell or a clonal population thereof from the individual chamber based on the response in the monitoring step.

Ex. 1001, 31:62–32:9 (Petitioner’s reference letters added).

Petitioner argues five grounds for *inter partes* review, as summarized in the following table:

Ground	Claim(s) Challenged	35 U.S.C. § ²	Reference(s)/Basis
1	1, 6, 11, 19, 24, 26, 27, 30	102(a), (e)	Dimov ³
2	1, 6, 11, 19, 24, 26, 27, 30	103(a)	Dimov
3	1, 6, 11, 19, 24, 26, 27, 30	103(a)	Dimov, Kovac ⁴
4	1, 11, 16, 24, 26, 27, 30	103(a)	Park ⁵
5	1, 11, 16, 24, 26, 27, 30	103(a)	Park, Kovac

Pet. 8.

D. DECLARATORY TESTIMONY

Petitioner relies on two declarations of Dr. Carl Meinhart. Exs. 1002, 1039. Petitioner also relies on the declaratory testimony of Dr. Ingrid Hsieh-Yee to establish the date of public availability for certain references.

Ex. 1020.

Patent Owner relies on a declaration of Dr. Bruce K. Gale. Ex. 2012.

² 35 U.S.C. §§ 102, 103 (2006), *amended by* Leahy–Smith America Invents Act, Pub. L. No. 112-29 §§ 102, 103, sec. (n)(1), 125 Stat. 284, 287, 293 (2011) (effective Mar. 16, 2013). These versions of §§ 102 and 103 apply because the effective priority date of the ’408 patent (no later than July 7, 2011, *see* Ex. 1001, code (22)) is before the effective date of the AIA amendments.

³ Dimov et al., US 8,906,669 B2 (issued Dec. 9, 2014 from application filed Oct. 9, 2009) (Ex. 1003). Petitioner also includes, within this ground, published international and US versions of the application which, according to Petitioner, contain the same text as all citations to Dimov in the Petition. Pet. 6 & n.1 (citing Exs. 1004, 1005). We refer to these publications, collectively, as “Dimov.”

⁴ J.R. Kovac & J. Voldman, *Intuitive, Image-Based Cell Sorting Using Optofluidic Cell Sorting*, 79 Anal. Chem. 9321 (2007) (“Kovac,” Ex. 1007).

⁵ Joong Yull Park et al., *Single Cell Trapping in Larger Microwells Capable of Supporting Cell Spreading and Proliferation*, 8 Microfluidics & Nanofluidics 263 (2010) (“Park,” Ex. 1006).

III. GROUNDS OF THE PETITION

For the reasons below, we determine that Petitioner has not shown, by a preponderance of the evidence, that any claims of the '408 patent are unpatentable under the grounds of the Petition. Before analyzing these grounds in detail, we address two matters that will underlie our analysis: the level of ordinary skill in the art and the construction of the claim terms.

A. LEVEL OF ORDINARY SKILL IN THE ART

The level of ordinary skill in the pertinent art at the time of the invention is a factor in how we construe patent claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–1313 (Fed. Cir. 2005) (en banc). It is also one of the factors we consider when determining whether a patent claim would have been obvious over the prior art. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

To assess the level of ordinary skill, we construct a hypothetical “person of ordinary skill in the art,” from whose vantage point we assess obviousness and claim interpretation. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). This legal construct “presumes that all prior art references in the field of the invention are available to this hypothetical skilled artisan.” *Id.* (citing *In re Carlson*, 983 F.2d 1032, 1038 (Fed. Cir. 1993)).

Relying on Dr. Meinhart’s testimony, Petitioner argues that a person of ordinary skill in the art “would have had a bachelor’s degree in mechanical engineering, chemical engineering, biomedical engineering, molecular biology, (bio)chemistry, or an equivalent degree relevant to microfluidic biological cell analysis, and three to five years of experience with the construction of and application of microfluidic devices to cell

culture and analysis.” Pet. 8–9 (citing Ex. 1002 ¶ 40). Patent Owner does not contest Petitioner’s proposed level of ordinary skill in the art. *See* PO Resp. 3–4 (citing Ex. 2012 ¶¶ 19–20).

We find Petitioner’s uncontested articulation to be reasonable in light of the subject matter involved in the ’408 patent and its description of the relevant prior-art background. *See, e.g.*, Ex. 1001, 1:15–2:54 (describing the field and related art as relating to the construction and use of microfluidic devices in cell culture and analysis). Thus, we adopt it for our decision.

B. CLAIM CONSTRUCTION

In an *inter partes* review, we construe a patent claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2020). This generally includes “construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.* “[W]e look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–1317).

The ordinary and customary meaning of a claim term “is its meaning to the ordinary artisan after reading the entire patent,” and “as of the effective filing date of the patent application.” *Phillips*, 415 F.3d at 1313, 1321. There are only two circumstances in which we adopt a construction that departs from the ordinary and customary meaning: “1) when a patentee sets out a definition and acts as [their] own lexicographer, or 2) when the

patentee disavows the full scope of a claim term either in the specification or during prosecution.” *Thorner v. Sony Comput. Entm’t Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). Any such special meaning of a term “must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention.” *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998).

Petitioner contends that “no terms require express construction for purposes of resolving the challenges in this proceeding.” Pet. 9; *accord* Pet. 12. Petitioner also notes that in the parallel district court proceedings, Patent Owner has proposed constructions for the terms *chamber* and *retaining position* that differ from Petitioner’s proposed constructions. Pet. 9–10 (citing Ex. 1013 App’x A, 1, 3 (Patent Owner’s proposed constructions); Ex. 1021, 7, 8 (Petitioner’s proposed constructions); Ex. 1002 ¶ 44). In those proceedings, Patent Owner’s proposed construction for *chamber* is “an enclosed space within a microfluidic device,” and its proposed construction for *retaining position* is “a location in the chamber at which a cell is maintained during cell culture and media exchange.” Ex. 1013, 6, 8. Although Petitioner does not contend that its arguments rely on the choice of construction for these terms, Petitioner adopts Patent Owner’s constructions for this proceeding. Pet. 11. Patent Owner does not contest these proposed constructions, or propose any other explicit constructions. *See generally* PO Resp.

We agree with Petitioner that we do not need to construe the terms *chamber* and *retaining position* to decide the issues presented in this proceeding, and to the extent we need to interpret the meaning of any claim

language, we address the interpretations below in the context of the prior art. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy’” (quoting *Vivid Techs., Inc. v. Am. Sci & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

C. GROUND S BASED ON DIMOV ALONE (GROUND S 1 AND 2)

In Grounds 1 and 2, Petitioner contends that Dimov anticipates claims 1, 6, 11, 19, 24, 26, 27, and 30, or alternatively that the claims are obvious over Dimov. *See* Pet. 12–40.

1. *Overview of Dimov*

Dimov describes “a microfluidic device having a fluid path defined within a substrate between an input and an output,” such that “particles provided within a fluid flowing within the fluid path will preferentially collect within the capture chamber.” Ex. 1003, code (57).

Figure 2, reproduced below, illustrates the overall microfluidic device:

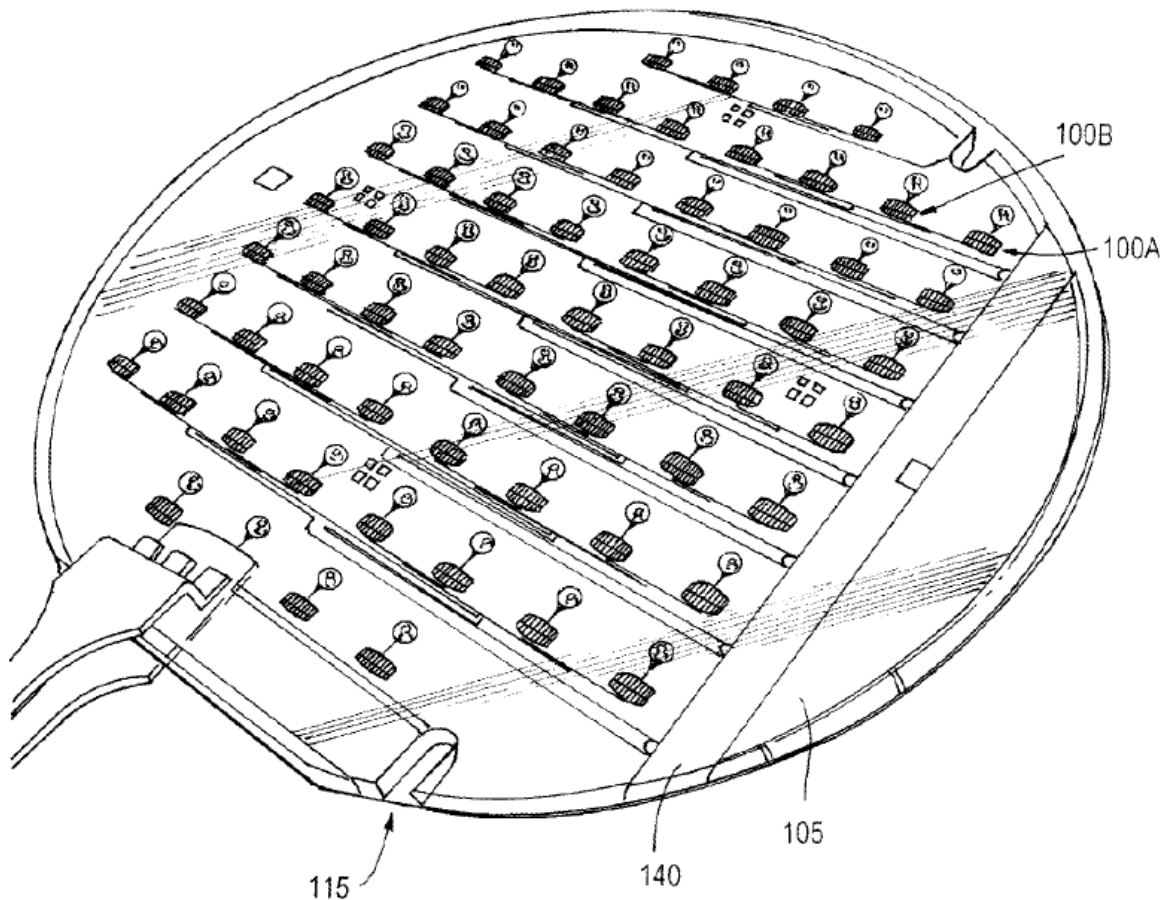


FIG. 2

Figure 2, above, depicts identical microfluidic devices 100 (100A, 100B, and many others) formed within substrate 105, and a multiplexed structure by which waste fluids are collected in common waste 140. *See* Ex. 1003, 2:29–30, 3:22–24, 3:54–57, 4:20–22. In use, substrate 105 is situated horizontally. *See id.* at 3:37–41.

Figure 1, reproduced below, shows microfluid device 100 (A or B) in more detail:

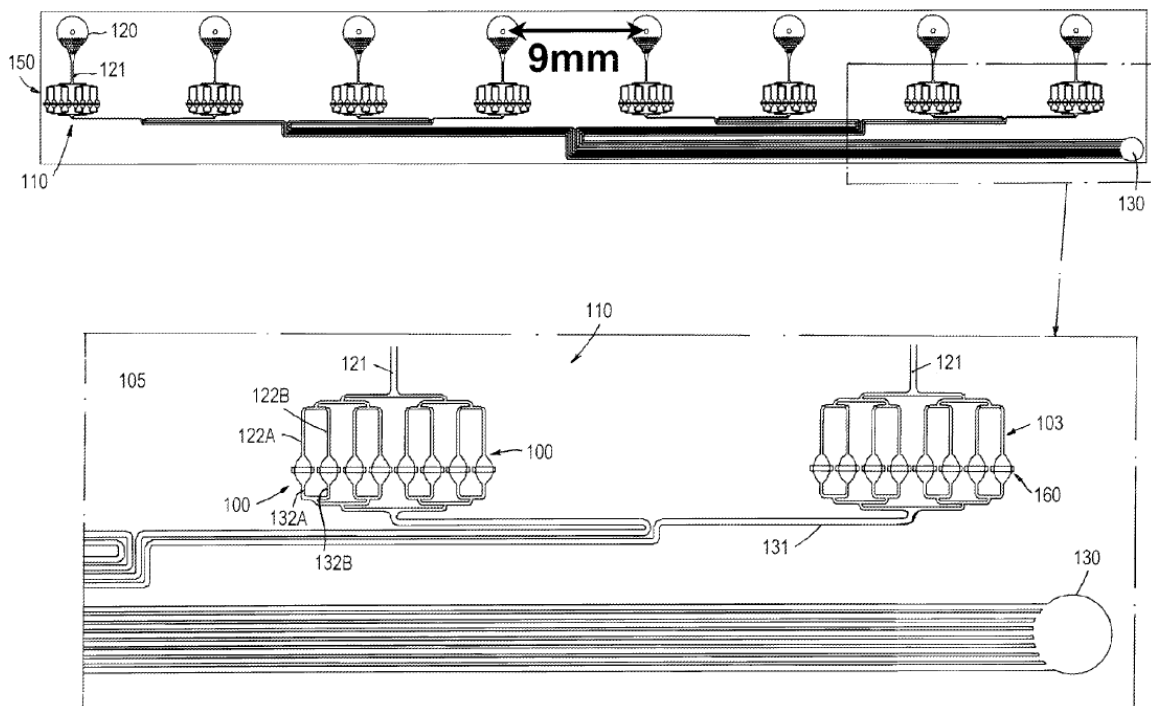


FIG. 1

As shown in Figure 1, above, each microfluidic device 100 “comprises a fluid path 103 defined within a substrate 105 between an input 120 and an output 130.” Ex. 1003, 3:24–26. Capture chambers 160 are also situated within fluid paths 103 and extend perpendicularly into substrate 105 so that cells passing through fluid path 103 are captured in chambers 160 by the downward pull of gravity. *See id.* at 3:27–53. Outputs 130 for each row empty into common waste 140 (shown above in Figure 2). *Id.* at 4:20–22.

Figure 4B, reproduced below, shows an individual capture chamber 160 within the microfluidic device:

depth of 320 μm , *id.* at 9:16–17. Dimov teaches that one benefit of these relatively large dimensions is that the device “can be usefully employed in biomimetic experiments” such as three-dimensional layered structures. *Id.* at 11:5–21.

An example of such three-dimensional layered structures is shown in Figure 21, reproduced below:

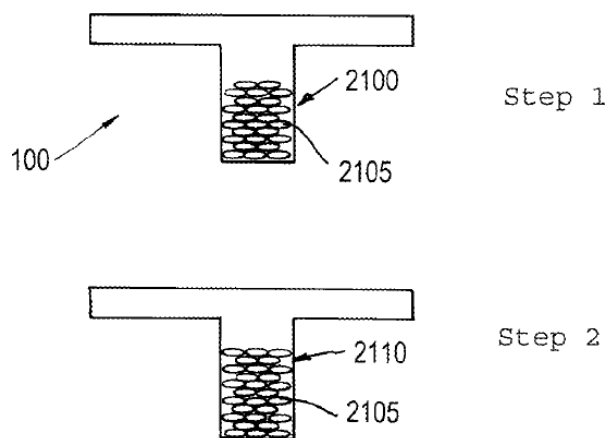


FIG. 21

Figure 21 of Dimov, above, depicts device 100 that “can be used to generate 3D cell structures 2100 of individual cancer cells 2105 so as to recreate cellular conditions similar to in-vivo tumours or other structures.” Ex. 1003, 11:7–10. According to Dimov, layered cells 2105 are typically “retained in the order that they were introduced into the chamber,” which “allows for subsequent experiments to be conducted within pseudo in vivo conditions.” *Id.* at 11:19–21.

Dimov states that “the arrangements described herein preferentially retain the particles within the trench.” Ex. 1003, 11:21–23. Alternatively, Dimov also teaches that

[i]t is possible to modify the arrangement so as to provide for subsequent movement of the particles—either within the trench so as to provide for mixing or the like, *or to effect removal of the particles out of the trench*. Such arrangements will typically require a capacity to manipulate the particles and this can be conducted either before or subsequent to capture of the particles within the trench. Examples of techniques that could be employed include:

- Acoustic
- Magnetic
- Inertial
- Electric
- Dielectrophoretic
- Thermo-hydrodynamic
- Laser tweezers*
- Hydrodynamically induced agitation
- Specific or unspecific attachment to surface

It will be understood that the use of such techniques may require an external source of agitation or manipulation of the particles.

Id. at 11:23–43 (emphasis added). Thus, Dimov lists a number of techniques, including “[l]aser tweezers,” for mixing or removing particles in a trench.

See id.

2. *Uncontested Limitations 1A–D*

Petitioner contends that Dimov discloses the preamble and limitations 1A–D, and points to passages within Dimov describing retaining a cell in a chamber, perfusing the cell with fluid while the cell is retained in the chamber, and culturing the cell within the chamber while monitoring a response. Pet. 13–26 (citing Ex. 1003, 1:40–47, 1:52–53, 1:57–60, 2:25–27, 2:33–36, 3:37–41, 3:47–53, 5:10–24, 5:27–35, 6:37–47, 7:4–20, 7:24–28, 8:16–18, 8:40–42, 9:32–48, 10:10–11, 10:55–58, 12:13–19, 12:66–13:3,

13:11–18, 13:23–42, 13:59–67, 14:1–6, 14:8–10, 14:13–17, 14:26–56, 15:1–13, 15:20–26, 16:4–7, Figs. 4B, 6, 7, 24; Ex. 1002 ¶¶ 54–84).

Patent Owner does not dispute Petitioner’s allegation that Dimov discloses limitations 1A–D. *See generally* PO Resp. We need not address Petitioner’s allegations regarding the preamble or limitations 1A–D because we determine, below, that Dimov does not disclose or teach limitation 1E.

3. *Asserted Anticipation by Dimov*

Limitation 1E recites “selectively recovering the cell or a clonal population thereof from the individual chamber based on the response in the monitoring step.” Ex. 1001, 32:7–9. In arguing that Dimov anticipates claim 1, Petitioner contends that Dimov discloses limitation 1E by listing various techniques, such as “[l]aser tweezers,” that can be used “within the trench to provide for mixing or the like, *or to effect removal of the particles out of the trench.*” Pet. 27 (quoting Ex. 1003, 11:21–26) (citing Ex. 1002 ¶ 85).

Petitioner argues that because “Dimov refers to removal of the particles out of an individual trench (‘the trench’), . . . Dimov discloses selectively recovering the individual cell, or a clonal population thereof, from the individual chamber.” Pet. 28 (citing Ex. 1002 ¶ 88). According to Petitioner, a person of ordinary skill in the art “would have understood that at least some of the [listed] techniques, such as laser tweezers, are techniques that, by their very natures and because of their technical limitations, would necessarily be directed to individual trenches.” Pet. 28 (citing Ex. 1002 ¶ 89).

Petitioner also argues that Dimov motivates “subsequent analysis or experimentation” within the chamber after loading the cells into the device,

and a person of ordinary skill in the art would have had the same motivation to remove the cells from the device for later analysis or experimentation. Pet. 29 (quoting Ex. 1003, 12:18) (citing Ex. 1003, 11:29–30, 12:13–18; Ex. 1002 ¶ 90). According to Petitioner, a person of ordinary skill “would have at once envisaged basing the removal of the cell on the response in a monitoring step.” Pet. 29 (citing *Kennametal, Inc. v. Ingersoll Cutting Tool, Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015); Ex. 1002 ¶ 91); *see also* Pet. 29–30 (citing Ex. 1002 ¶¶ 92–92) (giving examples of reasons why a person of ordinary skill would have envisioned removing cells for further analysis).

In its Response, Patent Owner contends that Dimov fails to disclose either “selectively recovering cells” or a “mechanism by which a cell could be recovered.” PO Resp. 5 (citing Ex. 2012 ¶¶ 24–38, 58–68). Patent Owner argues that all the specific examples in Dimov are directed to the embodiment in which cells are retained in the trenches and analyzed by exposing them to different fluids and conditions while they are still in the trenches. *See id.* at 5–6 (citing Ex. 1003, 7:30–39, 8:4–9, 10:11–12, 10:55–58, 11:1–21, 12:13–18, 13:43–46; Ex. 2010, 161:11–24; Ex. 2012 ¶¶ 23–37, 58–69). Indeed, according to Patent Owner, Dimov contemplates that cell responses will be analyzed by exposing the cells “‘to a suitable lysis agent’ in the trenches so that they burst and ‘their contents may be released’ into the liquid media.” *Id.* at 7 (citing Ex. 1003, 7:37–41, 8:6–9; Ex. 2010, 173:21–174:5; Ex. 2012 ¶ 63).

Patent Owner also argues that Dimov fails to disclose, within its microfluidic device, any structure that would allow for the selective recovery of a cell or clonal cell population. PO Resp. 6–7. According to Patent Owner, “there is no direct access to the trenches, and all fluid leaving every

trench converges into a single common waste, from which cells cannot be selectively recovered.” *Id.* at 7 (citing Ex. 1003, 4:5–8, 4:18–22; Ex. 2012 ¶¶ 58–69); *see also id.* at 29–32. Relying on the testimony of Dr. Gale, Patent Owner argues that the lines leading out of each capture chamber are “very long and convoluted, which introduces additional complications such as loss of cells to interior walls, an inability to follow any specific cells of interest, significant dilution, shear stresses, and congestion, none of which support cell recovery.” *Id.* at 7 (citing Ex. 2012 ¶¶ 24, 30, 63). Further, to the extent that lysis agents are used in any of the experiments on the chip, Patent Owner contends that such agents would destroy any intact cells on their path to the common waste. *Id.* at 7–8 (citing Ex. 1003, 4:1–22, Fig. 1; Ex. 2010, 173:1–20; Ex. 2012 ¶¶ 32, 60–62).

Finally, Patent Owner argues that, while Dimov briefly discusses “removal” of particles from the trenches and a “generic list” of nine techniques for mixing or removal, the focus of Dimov “is on what is retained in the trench, not what is discarded or removed.” PO Resp. 8 (citing Ex. 2012 ¶¶ 59–69); *see also* Ex. 2012 ¶ 64 (Dr. Gale opining that Dimov’s mention of removal techniques relates to “removing waste or other unwanted particles out of the capture chamber/trench”⁶). According to Patent Owner, Dimov provides no disclosure, and no examples, about “(i) how specifically to employ the list of potential techniques, (ii) how to agitate or

⁶ Petitioner appears to interpret Dr. Gale’s testimony in paragraph 64 of his declaration as opining that the “particles” that Dimov mentions are not cells. *See* Pet. Reply 3–4. This is not how we interpret his testimony, and in any event, Dr. Gale agreed on cross-examination that in Dimov, the term *particles* may include cells. *See* Ex. 1038, 46:4–47:10.

manipulate the particles, [or] (iii) how to remove, much less selectively recover *individual* cells without damaging or otherwise altering the cells to be removed.” *Id.* at 8–9. Thus, Patent Owner disagrees with Petitioner that a person of ordinary skill in the art “would have at once envisaged” performing a selective cell recovery in response to monitoring a cell response in one of the chambers. *Id.* at 9–10 (quoting Pet. 29).

In its Reply, Petitioner contends that Patent Owner does not dispute that Dimov discloses at least some embodiments that could be used for removing cells from Dimov’s individual trenches, or “that removing particles from one of multiple trenches constitutes selectively recovering the particles.” Pet. Reply 2–3 (citing Ex. 1001, 26:57–62; Ex. 1003, 11:21–26; Ex. 2012 ¶¶ 37, 66; Ex. 1038, 123:17–125:10; Ex. 1039 ¶¶ 5–9). And according to Petitioner, Dimov’s example of using the trenches for biomimetic experiments is not the only disclosed embodiment, and Dimov frames the possibility of cell removal as an alternative embodiment. *Id.* at 3 (citing Ex. 2010, 205:19–206:11; Ex. 1039 ¶¶ 13–20).

Finally, Petitioner argues that Dimov’s disclosure is not inconsistent with selectively recovering cells because (a) Dimov’s disclosure about retaining and analyzing cells in the trenches does not preclude subsequently removing the cells (Pet. Reply 4 (citing Ex. 1002 ¶ 92; Ex. 1039 ¶¶ 21–30)); (b) Dimov does not teach that every single experiment in its devices will include the use of a lysis agent (*id.* (citing Ex. 1038, 56:2–5, 55:15–20; Ex. 1039 ¶¶ 49–51)); (c) limitation 1E does not impose any requirements on what happens to a cell after it is selectively recovered (*id.* (citing Ex. 1039 ¶¶ 21–30, 52–55)); (d) none of Dimov’s structural features, such as the common waste stream, “would prevent selective recovery” (*id.* at 5 (citing

Ex. 1039 ¶¶ 31–48⁷)); and (e) “Patent Owner fails to show that a [person of ordinary skill in the art] would have lacked the knowledge or skill to implement Dimov’s removal techniques—including laser tweezers, which was well known in the art” (*id.* (citing Ex. 1039 ¶¶ 11–12)).

To establish anticipation, a petitioner must find each and every element in a claim, arranged as recited in the claim, in a single prior art reference. *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). The limitations may be present in the reference “either explicitly or inherently.” *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Further, an anticipating prior art reference must be enabling and must describe the “claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention.” *See Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346 (Fed. Cir. 2000). We do, however, consider the reference “together with the knowledge of one of ordinary skill in the pertinent art.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citing *In re Samour*, 571 F.2d 559, 562 (CCPA 1978)).

Based on these principles, we agree with Patent Owner that Petitioner has not identified within the four corners of Dimov a sufficient disclosure of

⁷ Petitioner improperly cites these eighteen paragraphs (more than ten pages) from Dr. Meinhart’s reply declaration in support of this conclusory technical assertion, without any additional commentary. Our rules prohibit this type of incorporation of testimony by reference, and we do not consider the cited paragraphs in our analysis. 37 CFR 42.6(a)(3) (“Arguments must not be incorporated by reference from one document into another document.”); *Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12 at 9 (PTAB Aug. 29, 2014) (informative) (declining to consider “conclusory statements [in an expert declaration] for which the Petition does not otherwise provide an argument or explanation”).

selectively recovering a cell based on the response in the monitoring step. Although Dimov discloses non-selective recovery and briefly lists a few general techniques that might be used for either mixing or recovery, Dimov does not specifically indicate which of the techniques would be useful for recovery rather than just mixing, and Dimov does not explicitly disclose that any cell recovery would be selective. Nor has Petitioner shown that Dimov inherently discloses selectively recovering any particular cell that has been cultured and monitored, because, as Dr. Gale persuasively testifies, Dimov's removal techniques could, as far as a person of ordinary skill in the art would have known based on Dimov's disclosure, be merely for "removing . . . unwanted particles out of the capture chamber/trench." Ex. 2012 ¶ 64; *see also id.* ¶ 63 ("Dimov . . . may suggest removing cellular materials (rather than intact cells) after capture . . ."). In other words, given Dimov's general focus on performing experiments *within* the trenches and the lack of any specific disclosure about how or why to remove cells, Petitioner has not met its burden to show that Dimov's potential cell-removal techniques would have *necessarily* been based on a response of a specific cell being cultured and monitored in limitation 1D.

We also agree with Patent Owner that Dimov does not disclose any specifics about how to carry out a selective cell removal based on one of Dimov's listed techniques, such as laser tweezers. *See* PO Resp. 8–9. Nor does Petitioner meet its burden of showing that such a technique would have been within the ordinary skill in the art at the time of the claimed invention. "In order to anticipate, a prior art disclosure must also be enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation." *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424

F.3d 1347, 1355 (Fed. Cir. 2005) (citing *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1342 (Fed. Cir. 2005)). Given the labyrinthine outlet channels leading from Dimov's chambers to the common waste stream and Dimov's lack of any disclosure of a way to identify and extract cells in the outlet streams, we credit Dr. Gale's testimony that there would have been substantial obstacles to recovering any specific cells that had been liberated from a trench in Dimov's device. *See* Ex. 2012 ¶ 63. Petitioner has not shown that a person of ordinary skill in the art would have overcome those obstacles without undue experimentation.

Thus, the evidence of record does not support Petitioner's argument that Dimov discloses limitation 1E or, consequently, that claim 1 is unpatentable under 25 U.S.C. § 102 as anticipated by Dimov.

4. *Obviousness over Dimov*

Alternatively, Petitioner argues in Ground 2 that claim 1 would have been obvious over Dimov, in view of the background knowledge of a person of ordinary skill in the art. Pet. 34–35 (citing Ex. 1002 ¶ 106).

A claim is unpatentable under § 103(a) for obviousness if the differences between the claimed subject matter and the prior art are “such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). When a ground in a petition is based on a combination of references, we consider “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *Id.* at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

We base our obviousness inquiry on factual considerations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) any objective indicia of obviousness or non-obviousness that may be in evidence.⁸ *See Graham*, 383 U.S. at 17–18.

The main issue in dispute for this ground is whether there was a sufficient motivation and sufficient background knowledge in the art, at the time of the claimed invention, that a person of ordinary skill in the art would have modified Dimov’s device to introduce selective recovery as recited in limitation 1E. For the reasons below, we determine that Petitioner has not met its burden of persuasion on this issue by a preponderance of the evidence.

According to Petitioner, Dimov discloses both monitoring a response in the chamber and removing cells from the chamber, and persons of ordinary skill in the art would have been motivated to selectively remove cells based on the monitored response, as recited in limitation 1E, so that they could further investigate cells of interest cultured in the chamber (such as to sequence their DNA or to expand the cells by culturing). Pet. 35–36 (citing Ex. 1002 ¶¶ 107–110).

As with its anticipation ground, Petitioner contends that an ordinarily skilled artisan would have removed cells using used one of the techniques listed in Dimov, such as laser tweezers. Pet. 36 (citing Ex. 1003, 11:30–40).

⁸ Because neither party argues that there are objective indicia of obviousness or non-obviousness, this does not factor into our decision. *See generally* Pet.; PO Resp.; Pet. Reply; PO Sur-Reply.

In an alternative proposed modification, Petitioner argues that a person of ordinary skill in the art would have inserted a micropipette into a trench to aspirate one or more of the cells of interest for further analysis. Pet. 36 (citing Ex. 1003, 11:30–40; Ex. 1002 ¶ 111). Below, we address each of these alternative theories in turn.

(a) Modification of Dimov by Using Listed Removal Techniques

Petitioner’s first obviousness theory is that a person of ordinary skill in the art would have had reason to use one of the listed cell-removal techniques, such as laser tweezers, for selective cell recovery according to limitation 1E. *See* Pet. 36. As we note above, Petitioner asserts that the motivation for this modification would have been to conduct further investigations on the cells, which may, for example, involve sequencing or culturing. *See* Pet. 35–36 (citing Ex. 1002 ¶¶ 107–110).

In response, Patent Owner contends that, if a person of ordinary skill in the art wanted to conduct further investigations on cells outside of a fluidic device, the evidence does not show that they would have started with Dimov’s “lab on a chip,” which “was not designed for selective cell recovery, but rather to capture cells in its chambers and retain them there for further analysis, and there is no mechanism by which a cell could be recovered.” PO Resp. 11–12 (citing Ex. 1003, 7:30–37; Ex. 2010, 159:2–160:22 (Dr. Meinhart acknowledging that Dimov is an example of lab-on-a-chip technology); Ex. 2012 ¶¶ 23–37, 70–81); *see also id.* at 18 (citing Ex. 2012 ¶¶ 87–90). Moreover, Patent Owner contends that any motivation to conduct subsequent experiments on cells of interest is already met by Dimov’s teaching that subsequent experiments take place in the same trench,

without removing them. *Id.* at 21–22 (citing Ex. 1003, 8:8–10, 14:1–15:26; Ex. 2010, 186:22–187:2; Ex. 2012 ¶¶ 24–37, 58–69, 79–80, 87–118).

To allow for selective recovery, Patent Owner contends that a person of ordinary skill in the art would have had to essentially redesign Dimov’s device to allow for external access to the trenches. PO Resp. 12; *see also id.* at 13 (arguing that the Examiner accepted a similar argument about Dimov during prosecution). According to Patent Owner, persons of ordinary skill in the art would not have made such a modification unless we attribute them with impermissible hindsight. *Id.* at 14 (citing *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013)); *see also id.* at 17 (citing Ex. 2012 ¶¶ 88–90; *InSite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859–60 (Fed. Cir. 2015) (“Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.”)).

Patent Owner also argues that, while Dimov mentions removal of particles from the trenches, Dimov’s main focus is conducting experiments, and in particular, biomimetic experiments, fully within the trenches, and Dimov does not give any examples of selective cell recovery for further investigation. PO Resp. 18–19 (citing Ex. 1003, 7:30–37, 11:1–15, 11:21–43, Fig. 21; Ex. 2010, 159:2–160:22, 184:3–9 (Dr. Meinhart agreeing that Dimov does not provide specific examples of successful selective recovery of a cell), 206:12–18 (Dr. Meinhart agreeing that Dimov’s discussion of cell

removal occurs within the discussion of biomimetic experiments such as shown in Dimov's Figure 21⁹); Ex. 2012 ¶¶ 23–37, 87–90, 109–123).

Thus, according to Patent Owner, Dimov does not actually teach that its listed cell mixing or removal techniques would have been for further investigation of cells exhibiting a particular response. PO Resp. 19 (citing Ex. 1003, 11:1–29; Ex. 2012 ¶¶ 112–118). Rather, given the context, Patent Owner contends that the mixing or removal techniques would have been used to adjust the cell layers during biomimetic experiments; “[f]or example, cells placed in layers for the biomimetic experiments may have needed to be rearranged because they were out of place, or because the researchers wanted a new arrangement for additional experiments.” *Id.* (citing Ex. 2012 ¶¶ 112–118).

Patent Owner also argues that, because Dimov's device channels the outlet of hundreds of additional capture chambers toward a common waste line, and describes no other output mechanism, a person of ordinary skill in the art would not have considered Dimov's device to be a viable starting-point for a method of selective cell recovery, particularly if any of the concurrently running experiments involved the use of lysis agents. PO Resp. 19–21 & nn.4–5 (citing Ex. 1003, 1:30–36, 4:1–22, 4:50–61, 7:37–41, 8:6–9; Ex. 2010, 163:8–23, 173:1–174:5, 178:9–179:7, 179:13–23; Ex. 2012 ¶¶ 63, 92–99); *see also supra* Section III.C.3.

⁹ Petitioner points out that in the same cross-examination testimony, Dr. Meinhart “testified that the discussion of cell removal is *not limited to* biomimetic experiments.” Pet. Reply 3 (emphasis added) (citing Ex. 2010, 205:19–206:11; Ex. 1039 ¶¶ 13–20).

In its Reply, Petitioner disagrees that Dimov’s mention of cell removal is limited to biomimetic experiments, even though both discussions occur in the same paragraph. Pet. Reply 3. According to Petitioner, Dimov’s discussion of mixing or removal techniques “begins with general reference to ‘the arrangements described herein,’ i.e., in the specification, not just the immediately preceding discussion.” *Id.* (quoting Ex. 1003, 11:21–22).

Petitioner also disagrees that a person of ordinary skill in the art would not have started with Dimov to obtain a microfluidic device that can allow for selective recovery as recited in limitation 1E. *See* Pet. Reply 6–7. According to Petitioner, it is undisputed that Dimov “was designed to conduct monitoring and analysis within the device, and reported doing so successfully.” *Id.* at 7 (quoting PO Resp. 12) (citing Ex. 1039 ¶¶ 57–59).

As we discuss above in the context of Petitioner’s anticipation ground, we disagree with Petitioner that Dimov itself discloses limitation 1E. *See supra* Section III.C.3. We also find that Dimov’s limited reference to removal of particles from a trench would have been insufficient to teach a person of ordinary skill in the art to effectively recover a cell if their motivation is, as Petitioner alleges, to conduct further investigations on the cells by, for example, sequencing or culturing. *See* Pet. 35–36.

First, we agree with Patent Owner that Dimov’s device is not, without substantial modification that Dimov itself does not teach, designed for selective cell recovery. As Patent Owner persuasively argues, Dimov’s device is a “lab on a chip” designed in general to retain cells while performing multiple experiments, so Dimov’s design choices reflect that general purpose. *See* PO Resp. 11–12, 18, 21–22; *see also* Ex. 1003, 10:55–67 (teaching the benefits of “lab on a chip” technology which allows a user

to conduct sequential investigations within a single structure). This is, in particular, evidenced by the multiplexed outlet streams, which channel all outlets to a common waste stream 140 without any apparent regard for viable cell recovery. *See* Ex. 1003, Figs. 1–3.

In light of this design, Petitioner has not persuasively shown that a person of ordinary skill in the art would have inferred, from Dimov’s brief reference to “removal of the particles out of the trench,” a teaching to conduct further analyses outside of the device (such as culturing or sequencing) on cells determined to be of interest based on a prior analysis. Given that Dimov’s disclosure focuses on conducting sequential experiments on the same chip, we credit Dr. Gale’s testimony that a person of ordinary skill in the art may *at least* as plausibly have interpreted this passage to suggest “removing waste or other unwanted particles out of the capture chamber/trench.” Ex. 2012 ¶¶ 64–65; *see also* Ex. 1038, 46:18–47:4 (testifying that Dimov also discloses the use of beads within the trenches, which are also “particles”). Petitioner has not pointed to anything in Dimov specifically suggesting that the “particles” to be removed are cells of interest destined for later analysis.

Even if Dimov does suggest removing cells to conduct further analyses outside the device, the reference merely lists a set of techniques and provides no guidance on how to carry out such removal in a way that would still allow for further meaningful analysis of cells. *See* Ex. 1003, 11:21–43. Although Dimov mentions “laser tweezers” as part of its list, Dimov does not address the specifics of liberating a particular cell or its clonal population from the device using a technique such as laser tweezers. Nor is Dimov’s mention of laser tweezers sufficient to motivate a person of

ordinary skill in the art to remove cells from a trench for further analysis outside the device. Dimov also does not address the difficulties a person of ordinary skill in the art would face in finding and recovering a cell that has been ejected into Dimov's common waste stream.

Based on these considerations, we conclude that Petitioner has not persuasively shown that Dimov's brief mention of cell removal techniques provides sufficient motivation or teachings for a person of ordinary skill in the art to selectively recover cells of interest for further analysis outside the device.

(b) Modification of Dimov to Allow for Direct Access via Micropipette

Alternatively, Petitioner argues that, based on background knowledge in the art, a person of ordinary skill in the art would have modified Dimov's device "in a way that would permit the top layer of the device to be peeled back so a trench could be accessed directly." Pet. 36–37 (citing Ex. 1002 ¶ 112). According to Petitioner, Dimov already discloses that its device is constructed in two PDMS layers, and the modification would involve making these two layers "at least partially unbonded, permitting [the top layer] to be peeled back so as to allow direct access to the trench." Pet. 37 (citing Ex. 1003, 3:10–12, 5:37–39, 15:27–46, Fig. 25; Ex. 1002 ¶¶ 113–114). Petitioner also contends that Dimov does not actually teach bonding the two layers together. Pet. 38 (citing Ex. 1003, 15:44–45; Ex. 1002 ¶¶ 114–115).

For this peelable-layer embodiment, Petitioner also relies on Chao Han, et al., *Integration of Single Oocyte Trapping, In Vitro Fertilization and Embryo Culture in a Microwell-Structured Microfluidic Device*, 10 Lab on a

Chip 2848 (2010) (Ex. 1009, “Han”). Pet. 38–40. According to Petitioner, Han discloses a device with two PDMS layers, in which the upper layer can be peeled back to aspirate oocyte cells using a micropipette. *Id.* Petitioner contends that Han bears a “Received” date of May 5, 2010, which precedes the earliest filing date (July 7, 2010) to which the ’408 patent claims priority. Pet. 38–39 (citing Ex. 1002 ¶ 117); *see* Ex. 1001, code (60). Petitioner contends that it would have been obvious to modify Dimov by adopting Han’s peelable, two-layer structure, with a reasonable expectation of success. Pet. 40 (citing Ex. 1002 ¶¶ 113–114, 120).

Petitioner does not identify Han as one of the prior art references upon which the Petition bases its challenges. *See* Pet. 8. Additionally, as Patent Owner points out, Petitioner does not actually assert, in the Petition, that Han is prior art to the ’408 patent. PO Resp. 15–16. Indeed, we find that the evidence of record does not establish that Han is a prior art publication. Petitioner’s own declarant opines that Han’s earliest publication date was September 15, 2010 (for the online version). *See* Ex. 1020 ¶ 68. This is after the ’408 patent’s earliest priority date of July 7, 2010. Ex. 1001, code (60). As Patent Owner correctly points out, Petitioner has not challenged this earliest priority date as applicable to claim 1. PO Resp. 15–16; PO Sur-reply 7 n.2; *see also* Pet. 8, 38 (noting this priority date, without challenging it); Pet. Reply 9 (“Han arguably was published after the earliest potential priority date . . .”).

In its Reply, Petitioner argues that, even if it Dimov itself did not teach the use of a peelable top layer to allow for micropipetting, its argument is based not just on Dimov, but on the background knowledge of a person of ordinary skill in the art. Pet. Reply 8. Citing testimony of Dr. Meinhart,

Petitioner contends that partially bonded PDMS layers and using a micropipette were “well known in the art.” *Id.* (citing Ex. 1003, 8:36–40 (describing use of a pipette); Ex. 1007, 9327–28 (describing pipetting as “standard lab practice”); Ex. 1038, 39:7–22; Ex. 1039 ¶¶ 69–78).

Petitioner argues that, “regardless of its prior art status,” Han is still “probative of the fact that those skilled in the art would have been motivated to construct a microfluidic device in a way that allowed the top layer of the device to be peeled back to expose microwells with cells that could be selectively aspirated by micropipette.” Pet. Reply 9 (citing *Yeda Research v. Mylan Pharm. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018)).¹⁰

Patent Owner counters, and we agree, that Petitioner has not shown that the peelable layer in Han’s device reflects the background knowledge of a person of ordinary skill in the art at the time of the claimed invention. *See* PO Sur-reply 7–8. As Patent Owner correctly points out, Han describes its microfluidic device as being “*novel*,” and Han particularly distinguishes the ability of its device, which allows extraction of embryos directly from a microwell using partially-bonded PDMS layers, from previous devices known in the art, which “had to generate a backward flow to make embryos return to the inlet” so they could be extracted. *Id.* (quoting Ex. 1009, 2853).

¹⁰ Patent Owner challenges this Reply argument as untimely. *See* Paper 24; Paper 27, No. 12. Petitioner disagrees, citing parts of the record to which it is responsive. Paper 28, No. 12 (citing PO Resp. 15:4–16:2, 36 n.11; Ex. 2012 ¶¶ 84, 137; Dec. 18 n.8). We do not need to decide whether the argument was untimely under 37 CFR § 42.23(b) because, ultimately, we find the argument unpersuasive.

Thus, the evidence of record does not suggest that Han's peelable PDMS layers were known in the art before the date of the claimed invention, and Petitioner has not shown that Han's device reflects the background knowledge of a person of ordinary skill in the art at the relevant time. Consequently, we do not find Petitioner's proposed modification to Dimov to be persuasive.

5. *Conclusion as to Grounds Based on Dimov*

For the above reasons, we determine that Petitioner has not shown, by a preponderance of the evidence, that Dimov anticipates claim 1 or that claim 1 would have been obvious over Dimov.

Claims 6, 11, 19, 24, 26, 27, and 30 depend, directly or indirectly, from claim 1, and thus incorporate limitation 1E and its requirement of "selectively recovering the cell or a clonal population thereof from the individual chamber based on the response in the monitoring step." *See* Ex. 1001, 32:7–9, 32:23–25, 32:35–38, 32:58–61, 33:6–7, 33:10–14, 33:19–20. Petitioner's analysis of these claims addresses only the added limitations of each dependent claim and does not provide further argument that would remedy the deficiency in Petitioner's analysis comparing claim 1 to Dimov. *See* Pet. 30–34.

Thus, for the reasons given above as to claim 1, Petitioner has not shown that Dimov anticipates claims 6, 11, 19, 24, 26, 27, and 30, or that the claims would have been obvious over Dimov. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious.").

D. GROUND BASED ON DIMOV AND KOVAC (GROUND 3)

In Ground 3, Petitioner contends that claims 1, 6, 11, 19, 24, 26, 27, and 30 are unpatentable as obvious over Dimov in view of Kovac. *See* Pet. 40–45.

1. *Overview of Kovac*

Kovac describes “a microscope-compatible, array-based microfluidic cell sorting architecture centered around passive hydrodynamic trapping of cells and active release using the optical scattering force” (Ex. 1007, 9322) of “a focused infrared laser to levitate cells of interest from their wells into a flow field for collection” (*id.* at 9321). According to Kovac, such “sorting can be a way to select a desired starting population of cells of known characteristics or can be a tool to analyze the results of an experiment and isolate particularly interesting cells for further investigation.” *Id.* (footnote omitted).

Figure 1 of Kovac, which illustrates this cell sorting process, is reproduced below:

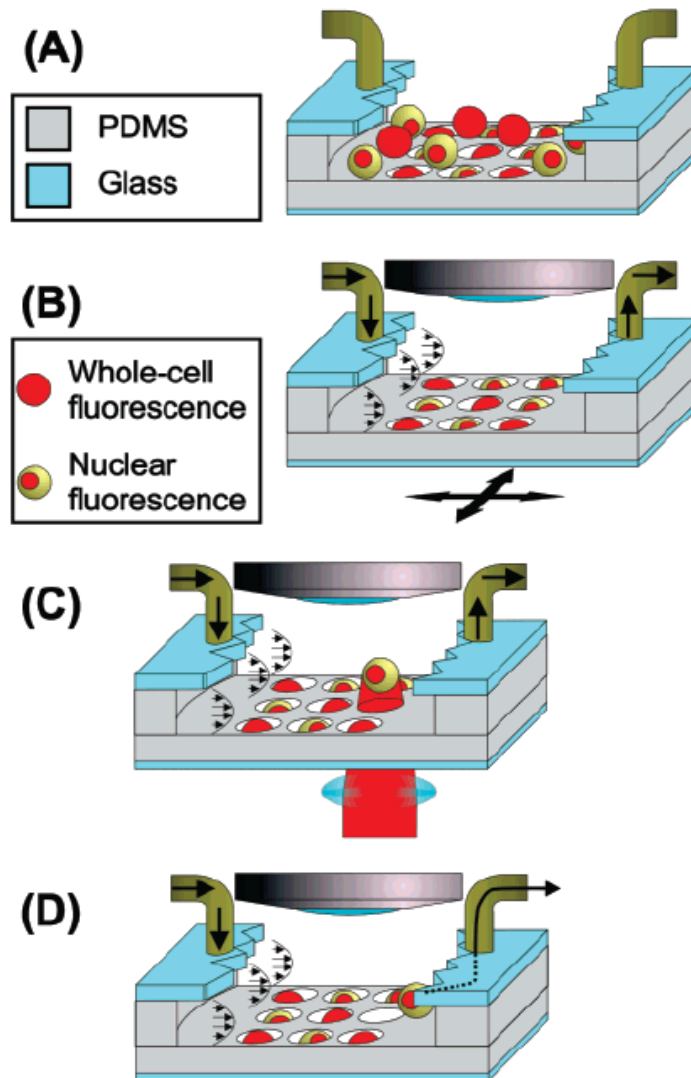


Figure 1, above, depicts a device with two glass layers between which is sandwiched a PDMS layer containing microwells, and above the microwells is a flow field in communication with a fluid inlet and a fluid outlet. *Id.* at 9322. The microwells are 30 μm wide and 35 μm deep, compared to a cell diameter of about 9 μm . *Id.* at 9326. The portion of the PDMS layer below the cells, through which the laser focuses, is about 2 mm thick. *Id.* at 9322–23, 9325.

As depicted in step (A), a fluid containing cells is injected into the device, and when the device is full, the flow is stopped while the cells sediment into the array while the fluid is stationary. Ex. 1007, 9322, 9324.

In step (B), the user pumps fresh media through the device, both forward and backward, and as a result, any cells remaining outside of wells, or which are trapped unstably in the array, flow away from the array and are removed. Ex. 1007, 9322, 9324. During this stage, the fluid outlet goes to an output waste stream. *Id.* at 9323 & Fig. 2.

In step (C), the system scans the entire array using software, and “[a]fter locating cells of interest, we focus an infrared (IR) laser beam onto target cells, levitating the cells into the flow field with the optical scattering force.” Ex. 1007, 9322, 9324–25. This levitation “effect is analogous to a beach ball being pushed vertically by a fire hose.” *Id.* at 9325. Kovac acknowledges a situation in which two cells could be stably trapped within the same microwell, and demonstrates that it is possible to remove one but not the other. *See id.* at 9326 & Fig. 3.

The width of the laser beam at its focal point is “roughly equal to the cell diameter ($\sim 9\text{ }\mu\text{m}$).” Ex. 1007, 9326. The laser has an output power of up to 150 mW and a wavelength of 980 nm, and is applied for up to about 30 seconds. *Id.* at 9324–25, 9327. Because of potential damage to the cells, the authors view this as “the most extreme parameters we would consider for cell removal.” *Id.* at 9327.

According to Kovac, this laser power and wavelength, beam width, and duration “is considerably gentler than parameters in many optical tweezers applications, where the beam is focused to micrometer-sized spots, sometimes at power levels up to $\sim 1\text{ W}$ for longer durations.” Ex. 1007, 9327.

Kovac compared these laser parameters to those in other studies and determined that one of the studies, which reported no cell damage using much higher laser power (13.2 W compared to 125 mW in Kovac) and a higher wavelength (1070 nm compared to 980 nm in Kovac) but much shorter exposure time (0.004 seconds compared to 20 seconds in Kovac) and much lower energy density (2.8×10^5 J/cm² compared to 4.3×10^6 J/cm² in Kovac) was also “an acceptable operating point.” Ex. 2004, Table S-1; Ex. 1007.

Finally, in step (D), as the cell is pushed into the flow stream, “[f]luid drag overcomes lateral optical forces, releasing the cell and washing it downstream for fractionation.” Ex. 1007, 9322. During this stage, the fluid outlet, with the liberated cell, goes to a reservoir output that can be pierced so that the cell can be removed with a pipette. *Id.* at 9323 & Fig. 2.

2. *The Parties’ Arguments*

For this ground, Petitioner relies on Dimov as teaching limitations 1A–D, as we discuss above in the context of the Dimov-only grounds. Pet. 40; *see supra* Sections III.C.3–4. In this ground, Petitioner relies on Kovac for teaching limitation 1E. *See* Pet. 40–41.

According to Petitioner, Kovac’s method selectively recovers cells by levitating them with a laser so that they “flow to a reservoir of the microfluidic device, where they are removed from the device by micropipette.” Pet. 42 (citing Ex. 1007, 9322; Ex. 1002 ¶ 125). In particular, Petitioner argues that an ordinarily skilled artisan would have used a microscope to inspect the trenches of Dimov’s device, and then would have “focus[ed] an infrared (IR) laser beam onto target cells from below through the glass substrate and bottom PDMS layer, as described in Kovac, levitating

the cells into the flow field with the optical scattering force.” Pet. 43 (citing Ex. 1007, 9322; Ex. 1002 ¶¶ 127–128). Petitioner notes that both the upper and lower layers of Dimov’s device are transparent, and the chambers would have been visible in either direction using a microscope. *See* Pet. 44 (citing Ex. 1003, 5:38–39, 6:6–14, 9:13–20, 9:23–27, Figs. 11, 13; Ex. 1002 ¶ 128).

Petitioner contends that, “after levitating a cell of interest from a [chamber] in the Dimov device, the levitated cell could then be flowed down ‘a fluid path 103 defined within a substrate 105’ to ‘an output 130’ . . . where it could then be removed from the device by micropipette.” Pet. 44 (quoting Ex. 1003, 3:22–26) (citing Ex. 1002 ¶ 128).

Petitioner argues that a person of ordinary skill in the art would have been motivated to modify Dimov’s device in this way given “the need to ‘select a desired population of cells of known characteristics’ or ‘isolate particularly interesting cells for further investigation.’” Pet. 43 (quoting Ex. 1007, 9321) (citing Ex. 1002 ¶ 126). According to Petitioner, Kovac teaches that its method “was straightforward, user-friendly, and conceivably automatable,” and that it “was simple to implement in a standard microscope with minimal modification.” *Id.* (citing Ex. 1007, 9325). Petitioner also argues that a person of ordinary skill in the art “would additionally have been motivated to combine Dimov with Kovac as described above because Dimov expressly discloses removing particles, such as cells, from trenches using ‘[d]ielectrophoretic’ and ‘[l]aser tweezers’ techniques, . . . and Kovac uses similar techniques to accomplish its ‘selective levitation.’” Pet. 44 (quoting Ex. 1003, 11:36, 11:38) (citing Ex. 1002 ¶ 130).

Finally, Petitioner contends that there would have been a reasonable expectation of success in combining Dimov with Kovac because “Kovac

discloses that experimental results confirmed that the selective levitation technique yielded the ‘expected viability given our optical parameters,’ and that ‘[c]ell retrieval from the device requires a simple pipetting step, which is standard lab practice and unlikely to damage cells.’ Pet. 45 (alteration in original) (quoting Ex. 1007, 9327–28) (citing Ex. 1007, 9328; Ex. 1002 ¶ 131).

In its Response, Patent Owner first argues, as discussed above in the context of Ground 2 based on Dimov, that if the motivation is to recover cells of interest for later analysis, a person of ordinary skill in the art would not have started with Dimov, which unlike Kovac describes a “lab on a chip” for performing sequential experiments within the same microfluidic device. *See* PO Resp. 17–22; *supra* Section III.C.4(a). According to Patent Owner, to the extent that Kovac provides motivation to sort and isolate cells of interest, using Kovac to provide a motivation to use of Dimov’s apparatus shows an improper hindsight bias, as “the Dimov device was simply not designed for selective cell recovery (let alone with the laser technique described in Kovac.” PO Resp. 22–23 & n.6 (citing Ex. 2010, 16:9–19, 17:4–9 (Dr. Meinhart agreeing that he did not opine that the challenged claims were obvious over either Kovac alone or over Kovac in view of Dimov)). Patent Owner also contends that Petitioner has not shown “why a [person of ordinary skill in the art] would have focused on selective cell recovery over [the] many other problems” known in the art at the time of the claimed invention. *Id.* at 17.

In its Reply, Petitioner contends that the need for selective cell recovery was known in the art, and that Dimov would have been an appropriate starting point for that endeavor. Pet. Reply 10. According to

Petitioner, the '408 patent admits that “[c]ell recovery is often required to enable functional assays to be performed on the progeny of the input cells, or to select cells of interest for larger scale culture. A method to recover defined clonal populations is therefore a critical requirement for many applications of microfluidic cultures.” *Id.* at 10–11 (quoting Ex. 1001, 26:1–6) (citing Ex. 1015, 42 (application as filed)). According to Petitioner, “[s]uch ‘applicant admitted prior art’ (AAPA) may be used to furnish a motivation to combine.” *Id.* at 11.¹¹ Petitioner also contests that it need not specifically establish why “selective cell recovery,” over any other problems, was the motivating reason to modify Dimov’s device. *Id.* (citing *KSR*, 550 U.S. at 420).

Next, Patent Owner disagrees with Petitioner that Dimov’s mention of laser tweezers as a mixing or removal technique would have led a person of ordinary skill in the art to Kovac’s method, because Kovac’s laser levitation technique is not laser tweezers, and Kovac distinguishes its technique from laser tweezers. PO Resp. 23 (citing Ex. 2012 ¶¶ 115–118; Ex. 2010, 110:16–23 (Dr. Meinhart agreeing that Kovac distinguishes its laser levitation technique from “traditional optical tweezers”)); *see* Ex. 2012 ¶ 117 (Dr. Gale

¹¹ Patent Owner contends that Petitioner’s reliance on the AAPA is untimely because it first appears in the Reply. Paper 27, No. 2. Petitioner counters that this argument is responsive to statements in the Patent Owner Response that question whether Petitioner has established that a person of ordinary skill in the art would have been motivated to modify Dimov by the problem of selective cell recovery. *See* PO Sur-reply 10 n.4; Paper 28, No. 2 (citing PO Resp. 2:12–18, 16:16–18, 17:5–15). Because Petitioner’s AAPA argument is not material to our analysis, as discussed below, we need not determine whether the argument was timely. *See infra* note 14.

testifying that “[t]he laser levitation approach proposed by Kovac does not trap particles, as occurs in laser tweezers, but rather balances particles on a column of laser light, meaning the particles are not held tightly in three dimensions.”). According to Patent Owner, Kovac makes modifications to its microwells to achieve its laser levitation technique, such as treating the walls to reduce cell adhesion, that are incompatible with Dimov’s goal of allowing for biomimetic experiments that require cell adhesion. PO Resp. 24 (citing Ex. 2012 ¶¶ 109–114).

Petitioner counters that Dimov’s reference to laser tweezers need not be so specific as to teach “Kovac’s particular mode of laser tweezers” to establish a motivation to combine with Kovac, because Dimov would have encompassed any form of laser tweezers known in the art. Pet. Reply 12 (citing Ex. 1039 ¶¶ 142–148). Relying on Dr. Meinhart’s testimony and some of the wording in Kovac, Petitioner disagrees that Kovac’s laser levitation method is not a form of laser tweezers. *Id.* (citing Ex. 1039 ¶ 145). Petitioner also argues that “nothing in Dimov requires cell adhesion,” so nothing about Kovac’s efforts to prevent adhesion during cell recovery would be incompatible with Dimov’s goals. *Id.* at 12–13 (citing Ex. 1039 ¶¶ 138–141).

Next, Patent Owner argues that the size of the trenches in Dimov’s microfluidic device is incompatible with Kovac’s laser levitation technique because the laser in Kovac’s device is focused in such a way that, “[a]s the cell is levitated away from the laser focus, the local intensity and lateral gradient force drop due to beam divergence.” PO Resp. 24 (alteration in original) (quoting Ex. 1007, 9326). Patent Owner contends that this would be an unsolved problem in Dimov’s device because “the cells in Dimov,

according to Petitioner, must be levitated to a height about ten times that in Kovac before they can exit the trenches.” *Id.*; *see also id.* at 29.

Patent Owner also argues that, because of the large increase in the distance that cells would have to be levitated in Dimov’s much deeper trenches, this “would require prolonged and/or increased exposure to lasers, increasing the risk of damage to the cell.” PO Resp. 24–25 (citing Ex. 1007, 9327; Ex. 2004; citing Ex. 2012 ¶¶ 55–56, 102–107, 122–123, 167, 169–170); *see also id.* at 29 n.7 (citing Ex. 2012 ¶¶ 105–107, 170) (arguing that Dr. Meinhart recognized that “avoiding damage to the cell is crucial to success of selective recovery” by framing a reasonable expectation of success in terms of what was “unlikely to damage cells” (citing Ex. 1002 ¶¶ 131, 182)).

Additionally, according to Patent Owner, neither Petitioner nor Dr. Meinhart has explained *how*, given how much larger Dimov’s trenches are than Kovac’s microwells, a person of ordinary skill in the art “would have gone about focusing an IR laser beam onto target cells to levitate the cell into the flow field of Dimov.” PO Resp. 27. Patent Owner argues that, on cross-examination, Dr. Meinhart was not able to say whether or not the “Dimov device’s deeper wells would require either prolonged or increased exposure to the IR laser compared to what we see in Kovac” because there are “a lot of factors at play” other than just the height of the trench. *Id.* at 27–28 (quoting Ex. 2010, 168:22–171:1, 171:14–15) (citing Ex. 2012 ¶¶ 92–99).

Patent Owner notes that Dr. Gale agrees with Dr. Meinhart that there are many factors at play, including trench depth, that would determine whether it would be possible to levitate cells from Dimov’s trenches using

Kovac's levitation technique. PO Resp. 28 (citing Ex. 2012 ¶¶ 92–99, 102–107, 119–128). Patent Owner also argues that Kovac is silent about how difficult it would be to implement its levitation technique on any other apparatus than its own, but notes that Kovac's model for describing the optical forces involved in levitation are so complex that “intuitive reasoning about behavior” is difficult. *Id.* (quoting Ex. 1007, 9325) (citing Ex. 2010, 100:6–20 (Dr. Meinhardt stating that for solving the optical equations for multiple cells, “it's very complicated to do [Kovac's optical calculations] analytically, but you could possibly do it numerically with computer simulations. And [Kovac] does not get into that detail because that's beyond the scope of this work.”)). As a result, according to Dr. Gale, a person of ordinary skill in the art would not be able to implement Kovac's levitation technique on a different device, such as Dimov's, by relying on Kovac's disclosure, and would have to conduct new experimental studies. *Id.* (citing Ex. 2012 ¶¶ 102–107, 122–128).

Petitioner counters that Patent Owner “does not substantiate [its] claims” that levitating cells out of Dimov's deeper wells would require prolonged exposure and increase the risk of cell damage. Pet. Reply 13 (citing Ex. 1039 ¶¶ 96–135, ¶¶ 149–151; Ex. 2012 ¶ 106). According to Petitioner, Kovac describes its laser parameters as benign, and the other references it cites use much harsher conditions. *Id.* (citing Ex. 1038, 100:9–101:10; Ex. 1039 ¶¶ 117–132). According to Petitioner, Kovac's data also suggests that the time periods or power levels of Kovac's levitation technique could be extended without causing cell damage, and none of the articles that Kovac cites “concluded that optical trapping techniques—even

harsh ones—should not be used for live-cell applications. *Id.* (citing Ex. 1039 ¶¶ 133–135).¹²

Petitioner also argues that Kovac’s teachings are not limited to its specific device, and points out that on cross-examination, Dr. Meinhart stated that so long as devices such as Dimov and Kovac are “submillimeter,” they would be comparable. Pet. Reply 14 & n.3 (citing Ex. 1007, 9329; Ex. 2010, 153:10–15; Ex. 1002 ¶¶ 102, 131). Petitioner also points to Dr. Meinhart’s cross-examination testimony that there is no need for Petitioner to “identify exact optical parameters and a precise exposure time for removing cells from one of Dimov’s trenches, and it would be no bar to obviousness if it were difficult to calculate such parameters, a priori, based on theory due to various factors.” *Id.* at 14–15 (citing Ex. 2010, 168:22–171:11). Petitioner ascribes such work to develop the combination of Dimov and Kovac as the ordinary creativity of a person of ordinary skill in the art. *Id.* at 15 (citing *Gen. Elec. Co. v. Raytheon Techs. Corp.*, 983 F.3d 1334, 1352 (Fed. Cir. 2020)). Petitioner argues that Patent Owner has not argued that experimentation would be undue or always required, and contends that, according to Dr. Gale, the experimentation would involve either increasing the exposure time or the laser power, but Petitioner denies that such alterations would result in cell damage. *Id.* at 15 (citing Ex. 2012 ¶ 104).

¹² Patent Owner contends that Petitioner has improperly incorporated by reference a large portion of Dr. Meinhart’s reply declaration without explanation. PO Sur-reply 10–11 n.5. We agree that Petitioner’s citations to paragraphs 96–135 and 149–151 (more than 27 pages) are insufficiently explained in the single paragraph on page 13 of Petitioner’s Reply. Thus, we do not consider this testimony apart from what Petitioner specifically points out in its Reply. *See* 37 CFR 42.6(a)(3).

Finally, Patent Owner argues that Petitioner has not persuasively shown that, given Dimov's labyrinthine outlet channels that converge from each trench, a person of ordinary skill in the art would have been able to successfully recover for future analysis any cell that has been liberated from Dimov's trench using Kovac's levitation technique. PO Resp. 29–32; *see also supra* Section III.C.3. According to Patent Owner, Dr. Meinhart agreed on cross-examination that in the proposed combination of Dimov and Kovac, the only modification to Dimov's shared output and common waste system would have been to use a "micropipette at the output to extract the cell." *Id.* at 30 (quoting Ex. 2010, 216:9–10) (citing Ex. 2010, 215:2–216:15).

But Patent Owner contends that this proposed modification to Dimov differs from Kovac's device, which includes a "reservoir output" where cells can be collected, separate from the "waste output." PO Resp. 30 n.8 (citing Ex. 1007, 9323–24; Ex. 2010, 67:23–68:25). Patent Owner argues that Petitioner has not explained how a person of ordinary skill in the art would track any cells liberated from the trenches so that they could be recovered somewhere in common waste outputs 130 or 140; for example, the cell would be outside the microscope's field of view. *Id.* at 30–31 (citing Ex. 1003, 4:5–8, 4:20–22, Figs. 1, 2, 4B; Ex. 2012 ¶¶ 63, 97–98, 124–128). According to Patent Owner, a person of ordinary skill in the art "would not have had a reasonable expectation of success following the cell through the device to identify the levitated cell for collection out of the 'common waste.'" *Id.* at 32 (citing Ex. 2012 ¶¶ 30, 97–98, 124–128).

Patent Owner points out that in Dimov's device, each trench shares a common input (120) with seven other trenches, so according to Patent

Owner, flushing a cell out of a trench would involve mixing the trench's outlet stream with fluid from the other neighboring trenches, which adds "a significant amount of fluid to flush the levitated cells through this long path," thus "further disturb[ing] the cell" and possibly mixing the cell with material from other trenches. PO Resp. 31–32 (citing Ex. 2012 ¶¶ 30, 97–98, 124–128). Relying on teachings of Kovac, testimony of Dr. Gale and an acknowledgement of Dr. Meinhart during cross-examination, Patent Owner contends that the convoluted outlet path in Dimov's device would result in "complications such as loss of cells to interior walls, an inability to follow any specific cells of interest, significant dilution, shear stresses, and congestion, none of which support cell recovery." *Id.* at 32 (citing Ex. 1007, 9329 ("[T]he number of contaminating cells collected varies directly with the total time during which target cells are removed."); Ex. 2012 ¶¶ 81, 97–98, 124–128; Ex. 2010, 120:13–121:5 (stating that, according to Kovac, "the longer you spend removing cells, . . . the higher the probability that spurious cells in that solution are collected"))).

Petitioner counters that Patent Owner has failed to show that a person of ordinary skill in the art would have been unable to recover levitated cells from Dimov's output stream. Pet. Reply 16 (citing Ex. 1039 ¶¶ 152–156). According to Petitioner, the Petition "never asserted that such monitoring would be required, and Patent Owner does not establish that a [person of ordinary skill in the art] could not accomplish such monitoring, if desired, by using a wider field of view or moving the microscope stage, for example."

Id. (citing Ex. 1039 ¶¶ 155–156).¹³ Petitioner also contends that “the challenged claims do not require 100% purity,” so the “speculation” that flushing the levitated cell into an outlet could result in mixing with other particles “does not defeat a reasonable expectation of success.” *Id.* (citing Ex. 1039 ¶¶ 157–158).

3. *Analysis*

Like Petitioner’s second ground, Petitioner asserts that the motivation to modify Dimov’s microfluidic device in view of Kovac’s levitation method would have been to allow a user to selectively recover cells of interest for later analysis outside the device. *See* Pet. 43 (identifying the motivation as “the need to ‘select a desired population of cells of known characteristics’ or ‘isolate particularly interesting cells for further investigation’” (quoting Ex. 1007, 9321)). For the reasons below, we find that Petitioner has not proven this motivation.¹⁴ Thus, Petitioner has not shown, by a preponderance of the evidence, that claim 1 would have been obvious over the combination of Dimov and Kovac.

¹³ Patent Owner contends that this argument is untimely because Petitioner first raised it in the Reply. Paper 27, No. 4; *see* Paper 28, No. 4 (Petitioner’s response). Because Petitioner’s assertion is not material to our decision, we do not need to decide whether it is untimely.

¹⁴ As discussed above, Petitioner alleges that the ’408 patent includes applicant admitted prior art (AAPA) establishing a known general motivation to selectively recover cells. *See supra* note 11; Ex. 1001, 26:1–6. We need not decide whether this passage is AAPA because, even if it were, it does not establish a motivation to combine Dimov and Kovac, specifically, to achieve the asserted goal of selective cell recovery.

First, we agree with Petitioner that its burden, under *KSR*, does not require it to show why selective cell recovery, over any other known problem in the art, would have been the motivating reason to modify Dimov's device. *See* Pet. Reply 11. *See KSR*, 550 U.S. at 420 (“[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.”). But “[a]lthough the *KSR* test is flexible, the Board ‘must still be careful not to allow hindsight reconstruction of references.’” *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016) (quoting *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1368 (Fed. Cir. 2012)). Petitioner must, at least, show that a person of ordinary skill in the art would have had reason to select Dimov's device as a suitable starting point to achieve what Petitioner contends is the motivating objective. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) (“[O]bviousness requires the . . . showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.”).

Second, we agree with Patent Owner that Petitioner has failed to meet its burden to show that a person of ordinary skill in the art would have selected Dimov's microfluidic device for use with Kovac's cell levitation method. That Dimov briefly mentions “[l]aser tweezers” as a possible mixing or removal technique (Ex. 1003, 11:38) is not persuasive evidence that a person of ordinary skill in the art would have selected Kovac's *specific* laser levitation method for use in Dimov's device to recover cells of interest for further analysis.

The evidence shows that the ability to recover useful cells, using laser-based manipulation, is highly dependent on the laser parameters, including power, exposure time, and the shape of the laser focus. *See, e.g.*, Ex. 1007, 9325–26; Ex. 2012 ¶ 104. For example, Kovac teaches that “[a]s the cell is levitated away from the laser focus, the local intensity and lateral gradient force drop due to beam divergence.” Ex. 1007, 9326; Ex. 2012 ¶¶ 50, 104. Although Kovac uses a beam divergence such that, despite this drop, maintains cells within the beam while levitating them into the flow stream above Kovac’s shallow 35 μm microwells (*see* Ex. 1007, 9326), Petitioner’s proposed combination would require focusing the laser beam such that it can raise a cell nearly an order of magnitude higher than in Kovac, and Petitioner has not shown how a person of ordinary skill in the art would have obtained laser parameters suitable for raising the cell that far.

Similarly, Petitioner has not shown how a person of ordinary skill in the art would have addressed the problem, discussed in Kovac, that under certain combinations of power, spot size, and exposure time, there is likely to be unacceptable cell damage that would motivate against using Kovac’s method in Dimov’s device to recover cells that are still usable for further analysis as per Petitioner’s alleged motivation to combine. *See* Ex. 1007, 9326–28; Ex. 2004, Table S-1. Kovac teaches that “the most extreme parameters [the authors] would consider for cell removal” in its 35 μm microwells are 150 mW applied to the cells for 30 seconds. Ex. 1007, 9327. But these parameters are designed for Kovac’s device, which uses a microwell that is nearly an order or magnitude narrower and shallower than Dimov’s trench.

Kovac teaches that, other than knowing that “scattering force is linearly proportional to power,” further intuitive reasoning about scattering behavior used in designing a laser levitation column is “difficult without focusing on a specific set of optical parameters.” Ex. 1007, 9325. Both Drs. Meinhart and Gale agree that there are “a lot of factors at play” when designing a laser column that could successfully levitate a cell into a flow stream without causing unacceptable cell damage. *See* Ex. 2010, 168:22–171:11; Ex. 2012 ¶¶ 92–99, 102–107, 119–128.

Yet, the uncontested level of ordinary skill in the art, which Petitioner proposed and we have adopted for this decision, involves only a bachelor’s degree and as little as three years of experience constructing and using microfluidic devices for cell culture and analysis. *See supra* Section III.A. Beyond that level of expertise, this articulation does not require any specialized knowledge of the use of lasers to manipulate living cells. We find that Petitioner has not shown, by a preponderance of the evidence, that such a person of ordinary skill in the art would have had the background knowledge and experience needed for manipulating the many “factors at play” to successfully adapt Kovac’s method for use in Dimov’s much deeper trenches. Nor has Petitioner demonstrated that it would have even been feasible to selectively recover cells from Dimov’s deep trenches that are suitable for future analysis outside Dimov’s device.¹⁵

¹⁵ Because we find that Petitioner has not persuasively proven its purported motivation to combine, we need not address the question of whether there would have been a reasonable expectation of success in modifying Dimov to achieve limitation 1E as claimed (which does not explicitly require the recovery of viable cells). *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge*

We also find that Petitioner has not shown that a person of ordinary skill in the art would have considered it feasible to recover liberated cells from Dimov's shared waste stream, given the long path from each trench to the waste stream and the fact that potentially hundreds of other trenches share the same outlet. *See supra* Section III.C.3 (discussing challenges that would be involved in recovering a specific cell from Dimov's device). Dimov's outlet is substantially different from that of Kovac, which has a single outlet for the array and a reservoir output, separate from the waste stream, where individual liberated cells travel to await recovery with a micropipette. *See Ex. 1007, 9322–23 & Figs. 1, 2A*. Given such differences and the lack of any such disclosure in Dimov itself, we determine that Petitioner has not explained, with enough specificity, how a person of ordinary skill in the art would have located and recovered a liberated cell from Dimov's common waste stream. *See Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017) (“[A] clear, evidence-supported account of the contemplated workings of the combination is a prerequisite to adequately explaining and supporting a conclusion that a relevant skilled artisan would have been motivated to make the combination and reasonably expect success in doing so.”).

For the above reasons, we determine that Petitioner has not shown, by a preponderance of the evidence, that claim 1 would have been obvious over Dimov in view of Kovac.

Ltd., 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (although reasonable expectation of success considers the invention as claimed, a skilled artisan's ability to achieve the intended outcome is relevant to the motivation to combine).

Beyond its arguments in the context of anticipation, Petitioner does not address the specific additional limitations of dependent claims 6, 11, 19, 24, 26, 27, and 30. *See* Pet. 40–45. Thus, for the reasons given above as to claim 1, Petitioner has not shown sufficiently that claims 6, 11, 19, 24, 26, 27, and 30 would have been obvious over Dimov in view of Kovac. *See Fine*, 837 F.2d at 1076.

E. GROUND BASED ON PARK (GROUND 4)

In Ground 4, Petitioner contends that claims 1, 11, 16, 24, 26, 27, and 30 are unpatentable under 35 U.S.C. § 103(a) as obvious over Park. *See* Pet. 45–61. As we discuss below, we determine that Petitioner’s arguments are not persuasive.

1. *Overview of Park*

Park is a journal article describing “a flow method that enables single cell trapping in microwells with dimensions of 50 μm , a size sufficient to allow attachment and division of captured cells.” Ex. 1006, 263. According to Park, prior studies had described methods for trapping multiple cells in each well, but “[s]ingle cell trapping is necessary to allow identification of differing cell phenotypes within a population of cells” and “enables observation of the direct descendants of single cells cultured under controlled biological conditions . . . , the analysis of intracellular compounds . . . , and the measurement of electrical functionality of cells.” *Id.*

Thus, Park designed a triangular microwell array configured so that, “[o]nce a cell is captured, the cell presence in the microwell changes the flow pattern, thereby preventing trapping of other cells.” Ex. 1006, 263. This is illustrated in Figures 1a–c of Park, reproduced below:

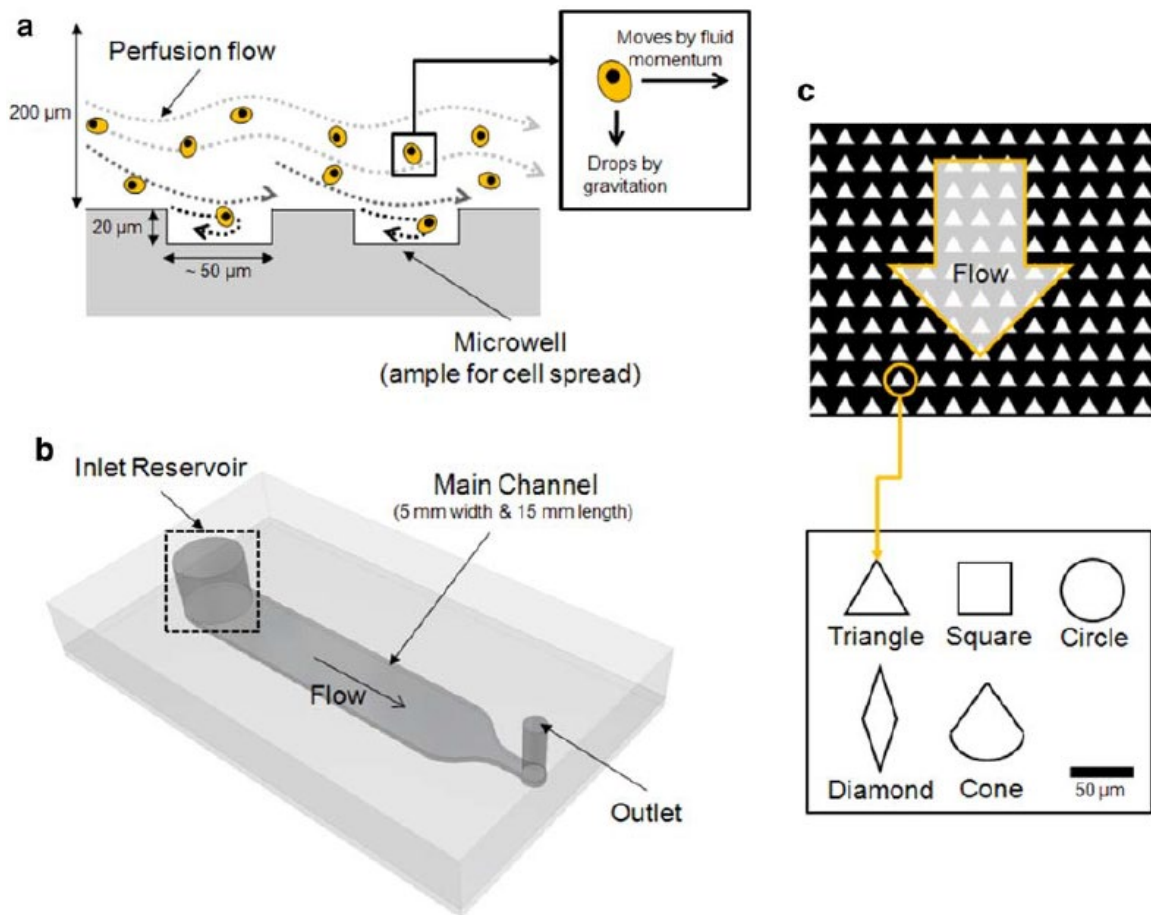


Figure 1b, above, shows the overall system, which includes an “inlet reservoir where the cell suspension is introduced, [a] main channel, microwells (not shown in the figure) patterned on the bottom surface of the main channel, and the outlet which is connected to a pulling syringe pump.” Ex. 1006, 264.

Figure 1a, above, is a cross-sectional view of the microwells (20 μm deep and 50 μm wide) and the main channel (200 μm deep). Ex. 1006, 264. “During the perfusion of cell suspension in the channel, the cells sink gradually due to gravity, and some cells are caught in microwells while others pass and are carried away by flow.” *Id.* at 264. According to Park, this is because, “[g]enerally, cells are 2–5% heavier than culture medium.” *Id.* at 265. “Depending on the velocity of the cell and its position relative to the

microwells, a cell may approach a threshold slow speed at which point gravity shifts the cell into a lower streamline that leads into a recirculation zone in the microwell.” *Id.*

Figure 1c, above, shows various microwell shapes that the authors tested in simulation, and shows the orientation of triangular microwells compared to the flow direction. *Id.* The authors “determined the equilateral triangle to be the best well shape because it had the strongest recirculation pattern in the microwell from 3D simulations.” Ex. 1006, 265–66.

After flowing the cell suspension across the array, the user can “flush the system . . . to remove excess cells” at a flow rate that “is fast enough to wash away untrapped cells, but slow enough not to dislodge trapped cells.” Ex. 1006, 268.

2. *Uncontested Limitations 1A–D*

Petitioner contends that Park discloses the preamble and limitations 1A–D, and points to passages within Park describing retaining a cell in a chamber, perfusing the cell with fluid while the cell is retained in the chamber, and culturing the cell within the chamber while monitoring a response. Pet. 45–57 (citing Ex. 1006, 264–68, Figs. 1–3; Ex. 1002 ¶¶ 132–159).

Patent Owner does not dispute Petitioner’s allegation that Park discloses limitations 1A–D. *See generally* PO Resp. We need not address Petitioner’s allegations regarding the preamble or limitations 1A–D because we determine, below, that Park does not disclose or teach limitation 1E.

3. *Limitation 1E*

For the selective recovery step of limitation 1E, Petitioner argues that because Park discloses culturing cells and monitoring responses in the triangular microwells, “[i]t would have been obvious to a [person of ordinary skill in the art] to make use of this monitoring by selectively removing one or more cells from an individual microwell based on a response—e.g., a long-term cell response or an instantaneous cell reaction—observed through such monitoring.” Pet. 57 (citing Ex. 1002 ¶ 160).

To accomplish this, Petitioner contends that a skilled artisan “would have found it obvious to construct the device of Park in a known way that would permit the top layer of the device to be removed or peeled back so a microwell could be accessed directly by micropipette.” Pet. 57 (citing Ex. 1002 ¶ 161). Petitioner contends that Park’s device has two layers, and although Park does not disclose what materials the layers are made of, “it would have been obvious to a [person of ordinary skill in the art] to make such layers from PDMS.” Pet. 57 (citing Ex. 1002 ¶ 162).

Because “Park does not state that the two layers of its device are bonded together,” Petitioner contends that this “suggest[s] that the top layer may actually be removable,” but even if Park’s top layer is not removable, according to Petitioner, an ordinarily skilled artisan “would have found it obvious to construct the device so that it would be removable or to partially bond the top layer to the bottom layer so the top layer could be peeled back to expose the microwell array.” Pet. 58 (citing Ex. 1002 ¶¶ 163–164).

As with its ground asserting obviousness based on Dimov, Petitioner relies on Han to support its proposed modification of Park’s device. *See*

Pet. 58 (citing Ex. 1009, 2849; Ex. 1002 ¶¶ 164–165); *supra* Section III.C.4(b).

In its Response, Patent Owner contends that nothing in Park suggests selectively recovering cells that had been trapped in its microwells based on a monitored response, or that Park’s device would have been suitable for such selective recovery of cells. *See* PO Resp. 33–37. In particular, Patent Owner contends that Park’s device was not designed for selective recovery, and focuses instead on ensuring that the microwells trap single cells yet still have space for subsequent attachment and division of captured cells within the microwells. *Id.* at 33–36 & n.10 (citing Ex. 1006, 263–65, 267, 268, Fig. 3c; Ex. 2010, 123:3–6; Ex. 2012 ¶¶ 46–47, 130–136).

According to Patent Owner, Park’s device did not “allow external access to the chambers,” so to allow for selective access to cells, a user would have had to redesign Park’s device in a way that has no basis within Park’s teachings. PO Resp. 36–37 (citing Ex. 1006, 265, 268 (“The main limitations of our system are . . . that a cover is required to create the channel, restricting access to the microwells during cell seeding”); Ex. 2012 ¶¶ 136–138). Thus, Patent Owner contends that Petitioner’s argument suffers from improper hindsight bias. *Id.* at 37 (citing *Cheese Sys.*, 725 F.3d at 1352). Patent Owner also contends that Petitioner’s reliance on Han for this teaching is improper for the same reasons it is improper in the context of Dimov’s disclosure. *Id.* at 36 n.11.

In its Reply, Petitioner counters that Patent Owner does not dispute that Park (1) is relevant prior art, (2) discloses limitations 1A–D, (3) is successful in culturing cells within the microwells, and (4) worked for its intended purpose. Pet. Reply 17. Petitioner also disputes Patent Owner’s

contention that Park discloses a closed system to which there is no direct access to microwells, because Park “implies the opposite when it discloses that the top layer or cover of its device merely ‘fits over’ the bottom layer, and notes that this ‘cover is required to create the channel, restricting access to the microwells *during cell seeding*.” *Id.* at 18 (quoting Ex. 1006, 265, 268). Petitioner contends that “[t]he qualification ‘during cell seeding’ would have suggested to a [person of ordinary skill in the art] that there is, in fact, access to the microwells at times other than during cell seeding.” *Id.* (citing Ex. 1039 ¶¶ 164–173).¹⁶ According to Petitioner, a skilled artisan would have displaced the cover to aspirate cells from a microwell via a micropipette. *Id.* (citing Ex. 1002 ¶¶ 160–165 (relying on Dimov and Han)).

We agree with Patent Owner that Petitioner has not pointed to anything in Park that teaches selectively recovering cells. Petitioner’s attempt to infer such a motivation from Park’s disclosure relies on improper hindsight bias. *See* PO Sur-reply 17–18. In particular, Park itself does not appear to motivate making the top layer removable and aspirating cells from microwells using a micropipette. At most, Petitioner has only shown why an ordinarily skilled artisan *could have* modified Park, not that there would have been actual motivation to make the proposed modifications. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (“obviousness concerns whether a skilled artisan not only *could have made* but *would have*

¹⁶ Patent Owner contends that this argument is untimely because it first appears in the Reply. Paper 27 No. 8; see Paper 28, No. 8 (Petitioner’s response). Because we ultimately find this argument unpersuasive, we need not decide whether it is untimely.

been motivated to make the combinations or modifications of prior art to arrive at the claimed invention”).

As to Petitioner’s reliance on Han as evidence that it was known in the art to make a microfluidic device peelable to allow access by a micropipette, we find this reliance insufficient for the reasons we discuss above in the context of the obviousness ground based on Dimov. *See supra* Section III.C.4(b); *see also* PO Resp. 18–20 (noting further distinctions between Park and Han).

For the above reasons, we determine that Petitioner has not shown, by a preponderance of the evidence, that claim 1 would have been obvious over Park. Petitioner’s arguments as to claims 6, 11, 16, 24, 26, 27, and 30 address only the added limitations of each dependent claim and do not provide further argument that would remedy the deficiency as to limitation 1E. *See* Pet. 59–61. Thus, Petitioner has not shown that these claims would have been obvious over Park. *See Fine*, 837 F.2d at 1076.

F. GROUND BASED ON PARK AND KOVAC (GROUND 5)

In its Ground 5, Petitioner contends that claims 1, 11, 16, 24, 26, 27, and 30 are unpatentable as obvious over Park in view of Kovac. *See* Pet. 62–63. For the reasons below, we determine that Petitioner has not proven unpatentability based on this ground by a preponderance of the evidence.

1. *The Parties’ Arguments*

For this ground, Petitioner relies on Park for teaching limitations 1A–D, as discussed above in the context of the Park-only ground (Ground 4), and relies on Kovac for teaching limitation 1E. *See* Pet. 62. According to Petitioner, a person of ordinary skill in the art “would have been motivated

to add the ‘selective levitation’ technique of Kovac, as described in [Petitioner’s third ground], to the methods disclosed in Park.” *Id.*

In particular, Petitioner contends that an ordinarily skilled artisan would have used a microscope to inspect Park’s microwells, and then would have “focus[ed] an infrared (IR) laser beam onto target cells from below, as described in Kovac, levitating the cells into the flow field with the optical scattering force.” Pet. 62 (citing Ex. 1007, 9322; Ex. 1002 ¶ 180). Petitioner contends that it would have been “obvious to use a transparent or semi-transparent material, such as PDMS, to construct the top layer of the Park device so as to permit visual observation of microwells from above.” Pet. 63 (citing Ex. 1002 ¶ 181). After levitating a cell, according to Petitioner, an ordinarily skilled artisan would then allow the cell to “flow[] down the ‘main channel’ to the existing ‘outlet,’ ‘which is connected to a pulling syringe pump’ to evacuate the cell from the device.” *Id.* (quoting Ex. 1006, 264) (citing Ex. 1002 ¶ 181).

Petitioner contends that Kovac’s microwells, 30 µm in diameter and 35 µm deep, are similar in size to Park’s microwells, 50 µm per side and 20 µm deep. Pet. 63 (citing Ex. 1007, 9326; Ex. 1006, 266). Petitioner also contends that Kovac teaches that its method would yield viable cells, and only requires a simple pipetting step to recover the cells. Pet. 63 (citing Ex. 1007, 9327–28).

In its Response, Patent Owner first argues that because Park’s device was not designed to allow for selective recovery of cells, “there would have been no reason for a [person of ordinary skill in the art] to have started with the Park device.” PO Resp. 38–39 (citing PO Resp. 33–37 (similar argument in the context of the ground based on Park alone); Ex. 2012 ¶¶ 139–159). As

with Dimov, Patent Owner contends that Park’s device “was designed to *trap* cells for culturing *within* the microwells of the device.” *Id.* at 39 (citing Ex. 2012 ¶¶ 41–46, 139–159). It is “a closed system having a single inlet and outlet” and “there was no way for a [person of ordinary skill in the art] to access the culturing cells without first disassembling the device and losing the flow through the device, which would allow any cells to end up back in the device.” *Id.* at 39–40 (citing Ex. 1006, 264–67; Ex. 2010, 142:6–8, 142:19–23; Ex. 2012 ¶¶ 44, 151–159); *see also id.* at 44 (citing Ex. 1006, 264–67; Ex. 2010, 142:6–8, 19–23; Ex. 2012 ¶¶ 52, 155–158) (noting that, unlike Kovac, Park has no outlet reservoir for recovering specific cells); *see also id.* at 53–54 (citing Ex. 2010, 141:14–16, 146:25–147:19, 150:18–151:2; Ex. 2012 ¶¶ 42, 155, 168) (arguing that Petitioner has not explained how a person of ordinary skill in the art would have modified Park’s device to allow for recovery of a specific liberated cell, other than disconnecting the syringe pump and thus disrupting the flow).

Next, Patent Owner argues that Petitioner has failed to show a motivation to combine Park with Kovac because, whereas Park’s device uses circulation patterns caused by fluid flow to trap cells within a well, “Kovac uses the lack of flow to trap cells, and does not discuss replication of cells in the wells” and “makes efforts to prevent the cells in its wells from becoming adhesive (by using suspension and pre-treating the wells), which is the opposite of Park’s goal.” PO Resp. 43 (citing Ex. 2010, 202:3–11; Ex. 2012 ¶¶ 45–46, 53, 147–149, 151–159); *see also id.* at 44 (citing Ex. 1006, 264–67; Ex. 2010, 83:23–84:5, 138:2–14, 142:6–8, 19–23; Ex. 2012 ¶¶ 42–46). Patent Owner argues that Park’s device is designed so that cells will attach to each other and to the wells during culturing, and Kovac contains no

teachings about using its levitation method under these very different circumstances. *Id.* at 49–50 (citing Ex. 1006, 267, Fig. 3c; Ex. 2002, 58:23–26; Ex. 2010, 117:12–119:7; Ex. 2012 ¶¶ 53–56, 161, 165).¹⁷

According to Patent Owner, “the triangular shaped microwells of Park were specifically designed to retain cells during flow,” yet in Kovac’s device, fluid flow is necessary for recovering any cells levitated by the laser. PO Resp. 47 (citing Ex. 1007, 9322; Ex. 2010, 89:8–11; Ex. 2012 ¶¶ 162–166). Thus, Patent Owner argues that in Petitioner’s proposed combination, “the dynamic flow of fluid through the microwells in Park would suppress the levitation force of the Kovac laser, hampering recovery.” *Id.* (citing Ex. 2012 ¶¶ 162–166). According to Patent Owner, counteracting this downward force “would require prolonged and/or increased exposure to lasers, increasing the risk of damage to the cell.” *Id.* at 48 (citing Ex. 2012 ¶¶ 55–56, 102–107, 122–123, 167, 169–170).

Next, Patent Owner points to other factors that would have complicated the proposed combination, such as that Park’s recirculation pattern drags cells not just downward but to an upstream corner where Stokes drag wall effects would have led to longer removal times from the microwell and failure of cell removal. PO Resp. 48 (citing Ex. 1006, 266–67, Fig. 2c; Ex. 1007, 9326 (“[N]onspecific surface interactions appear to be

¹⁷ Although Patent Owner acknowledges that Kovac discusses removing a single cell from a well with multiple cells, Patent Owner contends that this only relates to a doubly loaded cell in which the cells are not the result of replication due to culturing and are not adhered to each other. PO Resp. 43 n.15 (citing Ex. 1007, 9326; Ex. 2010, 221:4–222:4 (Dr. Meinhardt agreeing that this example in Kovac is for a single cell in a doubly loaded well); Ex. 2012 ¶¶ 148–149, 157).

the primary reason that cell removal fails.”); Ex. 2010, 115:5–117:11, 112:22–113:23, 139:5–9; Ex. 2012 ¶¶ 162–166).

Patent Owner also argues that Dr. Meinhart acknowledged that a person of ordinary skill in the art would have needed to modify the laser parameters, such as by using a different lens, to use Kovac’s levitation method in Park’s device. PO Resp. 50 (citing Ex. 2010, 132:9–136:12). And according to Patent Owner, Dr. Meinhart recognized that there were “a lot of factors at play” that would affect the levitation, such as “cell size, whether cells are conglomerated together, . . . wall interactions . . . recirculation patter[n]s, [and] hydrodynamic drag,” such that “[i]t’d be difficult to determine how much time would be necessary to be exposed.” *Id.* at 50–51 (first, second, and fourth alterations in original) (quoting Ex. 2010, 168:22–171:7). Patent Owner reiterates its arguments, discussed above in the context of combining Dimov with Kovac, that Kovac’s levitation technique involves complicated factors for which intuitive reasoning is difficult, so a person of ordinary skill in the art “would need to experiment to figure out if a cell could be levitated out of a well.” *Id.* at 51 (citing Ex. 1007, 9327; Ex. 2010, 100:6–20; Ex. 2012 ¶¶ 96, 120, 160–166).

Patent Owner also contends that if Kovac’s levitation method were used in Park’s device, any liberated cell would “need to pass over the array of other microwells before reaching the common outlet,” which according to Park are only 62% filled, leaving “approximately 40% of the microwells open and in which the levitated cell could be recaptured” by recirculation patterns caused by the flow necessary to extract a cell. PO Resp. 52–53 (citing Ex. 1006, 263–64; Ex. 1007, 9329; Ex. 2010, 120:13–121:5, 141:4–13; Ex. 2012 ¶¶ 167–170).

In its Reply, Petitioner disagrees that it would have been difficult for a person of ordinary skill in the art to use a different lens or otherwise adjust the laser parameters to adapt Kovac's levitation method for use in Park's device. Pet. Reply 23–24. Petitioner only acknowledges that there would be difficulty to say, “a priori, whether levitation out of deeper wells would take longer,” and contends that Kovac only stated that intuitive reasoning about its optical equations would be difficult to predict “without focusing on a specific set of optical parameters.” *Id.* at 23 (emphasis omitted) (quoting Ex. 1007, 9325). According to Petitioner, Dr. Meinhart testified that it would have been possible to adapt Kovac's technique “without actually calculating numbers from the equation.” *Id.* at 23–24 (quoting Ex. 2010, 100:2–5) (citing Ex. 1039 ¶ 149).

Petitioner also provides a number of further rationales for how a person of ordinary skill in the art would have modified Park's device to work with Kovac's levitation method.¹⁸ To address Patent Owner's argument that Petitioner has not explained how to recover specific cells from Park's device, Petitioner contends that an ordinarily skilled artisan would have sucked a liberated cell “directly into the pump's syringe” before disconnecting it. Pet. Reply 20 (citing Ex. 1002 ¶ 181, Ex. 1039 ¶¶ 184–188).

¹⁸ Patent Owner contends that these arguments are untimely, and we agree at least as to certain of the arguments. *See* Paper 27, Nos. 6, 9, 10; *see* Paper 28, Nos. 6, 9, 10 (Petitioner's responses). The new arguments introduce new theories as to how to combine Park and Kovac, including additional steps or new modifications necessary for a successful combination, which could have been presented in the Petition but were not. Nevertheless, as we discuss below, we find these arguments unpersuasive.

Petitioner also contends, for the first time, that a person of ordinary skill in the art would have addressed the problem of Park’s downward-forcing circulation patterns¹⁹ by starting with flow turned off and then turning on flow “after levitation begins, including after the cell has been pushed up out of a well high enough to be clear of recirculating flow lines created once it is turned on.” Pet. Reply 19–20 (citing Ex. 1039 ¶¶ 175–177); *see also id.* at 22 (citing Ex. 1039 ¶ 193).

Alternatively, Petitioner asserts that an ordinarily skilled artisan would have adjusted the size of Kovac’s laser column to cover Park’s entire triangular microwells, so that a cell would have no place to be pushed out of the laser column by the circulating flow. *See* Pet. Reply 21–22 (citing Ex. 1039 ¶¶ 190–196). Petitioner asserts that, because this wider beam would have lower power density, this would “*decrease* the risk of damage to the cell.” *Id.* at 22 (citing Ex. 1039 ¶¶ 193, 205–206).

On the issue of whether cell attachment associated with culturing of the cells in Park’s device would hamper the ability to levitate the cells, Petitioner acknowledges that Park “states that its wells are of ‘a size sufficient to allow attachment and division of captured cells.’” Pet. Reply 24 (quoting Ex. 1006, 263). But Petitioner asserts that “Park nowhere teaches

¹⁹ Petitioner contends that “Patent Owner fails to explain how resisting lateral movement would affect selective recovery by levitation, and does not establish that any resistance to vertical movement would be problematic either.” Pet. Reply 24 (citing Ex. 1039 ¶¶ 190–196). This improperly shifts the burden of persuasion onto Patent Owner. *See Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1379–81 (Fed. Cir. 2015) (a petitioner has the burden of persuasion in an *inter partes* review, which does not shift to the patent owner).

that its device can be used only with cells that attach within wells, let alone those that remain attached.” *Id.* (citing Ex. 1039 ¶¶ 180–183, 189).

As to the issue that cells liberated in Park’s device would have to pass over other empty wells that might recapture the cells, Petitioner responds that a person of ordinary skill in the art could simply repeat the process at the empty well that the cell fell into, which Petitioner contends would not require the use of extraordinary skill or creativity. Pet. Reply 25. Petitioner also argues that “the probability that a levitated cell will be recaptured is very low,” which Dr. Meinhart calculates as “about 13.8%.” *Id.* (citing Ex. 1006, 268; Ex. 1039 ¶¶ 197–204).

In its Sur-reply, Patent Owner contends that “there are no experiments performed in Park where the flow is turned on and off after cells are permitted to culture.” PO Sur-reply 22 (citing Ex. 2013, 358:25–359:9). Thus, Patent Owner contends that it is unknown whether “this would have resulted in additional cells dislodging when the flow was turned on and off for each attempt at selective cell recovery,” and “it is unknown how this may have affected the technique or cell health, including overheating due to the lack of cell medium exchange from the flow of the device.” *Id.* Patent Owner also contends that “Petitioner and Dr. Meinhart provide no mechanism for a [person of ordinary skill in the art] to have been able to determine when the cell was ‘high enough to be clear of recirculating flow.’” *Id.*

Similarly, Patent Owner contends that Petitioner’s proposed modification of disconnecting Park’s syringe after recovering a cell in the syringe also “would have required a [person of ordinary skill in the art] to turn on and off the flow of Park . . . , which would increase the number of

non-target cells dislodged.” PO Sur-reply 24 (citing Ex. 1039 ¶ 188). And Patent Owner contends that Petitioner “does not explain how a [person of ordinary skill in the art] would have been able to determine when the cell enters the pump so it could be disengaged for recovery.” *Id.* (citing Ex. 1038, 111:18–113:6).

Patent Owner also argues that Kovac teaches that the width of its laser column was “specifically selected to levitate a single cell from its microwell ‘without perturbing cells in neighboring wells.’” PO Sur-reply 23 (quoting Ex. 1007, 9325–26 (“We . . . demonstrated the feasibility of selectively levitating a single . . . cell from a microwell without perturbing cells in neighboring wells. We focused the beam so that the beam waist was roughly equal to the cell diameter ($\sim 9\text{ }\mu\text{m}$).”)). But according to Patent Owner, increasing the width of the laser column to cover Park’s entire microwell “would have disturbed cells in neighboring wells.” *Id.* Patent Owner also contends that if spot size increases to cover Park’s microwells (which are about $50\text{ }\mu\text{m}$ per side),²⁰ Dr. Meinhart acknowledges that this “will decrease the lateral gradient force,” but “Dr. Meinhart . . . did not consider how this reduction in force would affect the laser’s ability to levitate a cell in Park’s well successfully (especially with cultured cells through Park’s recirculation pattern).” *Id.* (quoting Ex. 2013, 344:18–345:5).

Finally, Patent Owner disagrees with the methodology of Dr. Meinhart’s estimate of a 13.8% probability that cells would be recaptured in

²⁰ Patent Owner contends that “Kovac already used a spot size that was ‘larger than those typically used.’” PO Sur-reply 24 (quoting Ex. 1007, 9325).

Park's microwells while passing over the array. PO Sur-reply 24–25. Even if the number is correct, Patent Owner contends, Kovac also discloses a loss of 18–28% of cells with its technique, so compounding the two losses from Park and Kovac “would have resulted in the loss of at least a third of the first cells that [were] successfully levitated.” *Id.* at 25 & n.11.

2. *Analysis*

Considering the evidence as a whole, we find that Petitioner has not met its burden to show obviousness based on the combination of Park and Kovac. As discussed above in the context of the combination of Dimov and Kovac, the evidence indicates that Kovac's laser levitation method is highly dependent on the laser parameters including power, exposure time, and the shape of the laser focus. *See supra* Section III.D.3. Petitioner's proposed modifications to Kovac's levitation method, such as substantially increasing the focused spot size (which was already “larger than those typically used in optical tweezers applications,” Ex. 1007, 9325), would have required substantial experimentation. Yet, as discussed above in the context of the Dimov–Kovac combination, the uncontested level of ordinary skill in the art only requires a bachelor's degree and 3–5 years of general experience constructing and using microfluidic devices for cell culture analysis. *See id.* Petitioner has not shown that such a person would have had sufficient background in using lasers to manipulate living cells that they could have adapted Kovac's levitation method for use in Park's device without additional inventive steps.

One particular complication would have been that Park's device is designed to create recirculating flow patterns whenever there is flow through the device (as is required in Kovac's method, *see* Ex. 1007, 9322, 9324–25;

Ex. 2012 ¶ 162), and we credit Dr. Gale’s testimony that these would have worked against any laser levitation. *See* Ex. 2012 ¶¶ 163–164; Ex. 1006, 266, Fig. 2a. We also credit Dr. Gale’s testimony that wall effects, or adhesion between cells and walls or other cells, would likely occur after culturing the cells in Park’s microwells,²¹ and would have been complicating factors for which neither Park nor Kovac provide solutions.²² *See* Ex. 2012 ¶¶ 161, 165.

We do not find persuasive Petitioner’s new argument in the Reply that, to address this complication, a person of ordinary skill in the art would have begun Kovac’s levitation procedure with fluid flow turned off, and then turned the fluid on at some point during the levitation where the flow pulling the cell into the fluid stream would be greater than the flow pulling it back into the microwell. Pet. Reply 19–20. Petitioner does not point to anything

²¹ Kovac does not appear to discuss the problems that would arise from levitating cells after culturing them in a microwell. Although Dr. Meinhart notes, in his deposition, that Kovac refers to “mitosis” (cell division) and the presence of two cells in a single well (*see* Ex. 2010, 219:3–220:7, 221:4–222:4), we find no reference in Kovac to levitation of cells that have been cultured within a microwell. Rather, Kovac refers to the asymmetrical shape of cells that had begun the process of mitosis at the time of levitation, and to the ability of removing two independent cells that had been trapped in the same chamber. Ex. 1007, 9326 (“Significantly aspheric cells, such as those undergoing mitosis, can be removed quickly, as their asymmetry makes them easier to remove via the fluid flow after they are levitated slightly.”); *id.*, Fig. 3 (demonstrating that it is possible to “remove a single targeted cell residing in a doubly loaded well”).

²² Kovac addressed this problem by treating the microwells to prevent adhesion. *See* Ex. 2012 ¶¶ 53–54; Ex. 1007, 9323–24, 9326. But Petitioner’s proposed combination does not include any surface treatment to Park’s microwells. *See* Pet. 62–63; Ex. 2010, 150:18–151:2.

in the prior art that would have suggested this further modification to Kovac's method, and does not explain how a person of ordinary skill in the art would have known when to turn on the fluid flow. *See id.*²³

Given the challenges that a person of ordinary skill in the art would have faced in adapting Kovac's cell levitation method for use in Park's very different microwells, and the lack of disclosure addressing these problems in either Kovac or Park, we find that Petitioner has not shown, by a preponderance of the evidence, that a person of ordinary skill in the art would have made the combination. Thus, we conclude that Petitioner has not shown that claim 1 is unpatentable as obvious over the combination of Kovac and Park.

For dependent claims 11, 16, 24, 26, 27, and 30, Petitioner relies on the teachings of Park and adds no further argument beyond the contentions in its obviousness ground based on Park alone (Ground 4). *See* Pet. 59–62. Thus, we find Petitioner's arguments as to these claims unpersuasive of obviousness and conclude that Petitioner has not shown these claims unpatentable. *See Fine*, 837 F.2d at 1076.

²³ According to Petitioner's combination, the user would be observing the microwells "from above." *See* Pet. 63; Ex. 1002 ¶ 181. Under these circumstances, it is unclear how the user would have been able to determine whether the cell has reached a sufficient height not to be pulled back into the microwell after flow resumes.

IV. CONCLUSION

For the reasons above, Petitioner has not shown by a preponderance of the evidence that any challenged claim of the '408 patent is unpatentable under any ground of the Petition.

V. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1, 6, 11, 16, 19, 24, 26, 27, and 30 of the '408 patent have not been shown to be unpatentable;

FURTHER ORDERED that parties to this proceeding seeking judicial review of our decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1, 6, 11, 19, 24, 26, 27, 30	102(a), (e)	Dimov		1, 6, 11, 19, 24, 26, 27, 30
1, 6, 11, 19, 24, 26, 27, 30	103(a)	Dimov		1, 6, 11, 19, 24, 26, 27, 30
1, 6, 11, 19, 24, 26, 27, 30	103(a)	Dimov, Kovac		1, 6, 11, 19, 24, 26, 27, 30
1, 11, 16, 24, 26, 27, 30	103(a)	Park		1, 11, 16, 24, 26, 27, 30
1, 11, 16, 24, 26, 27, 30	103(a)	Park, Kovac		1, 11, 16, 24, 26, 27, 30
Overall Outcome				1, 6, 11, 16, 19, 24, 26, 27, 30

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