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Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd
Santa Clara, CA 95051

EXAMINER
KAUP, SAHANA S

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JEFFREY R. SAMPSON, NICHOLAS M. SAMPAS, JOEL MYERSON, PAIGE ANDERSON, and BO CURRY

Appeal 2020-002151
Application 14/550,713
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to a method for high throughput gene assembly in droplets. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as Agilent Technologies, Inc. (*see* Appeal Br. 2).

[2] We have considered and herein refer to the Specification of Nov. 21, 2014 ("Spec."); Final Office Action of Jan. 25, 2019 ("Final Act."); Appeal Brief of July 23, 2019 ("Appeal Br."); Examiner's Answer of Nov. 18, 2019 ("Ans."); and Reply Brief of Jan. 21, 2020 ("Reply Br.").

Statement of the Case

Background

"High-throughput synthesis and assembly of DNA constructs is an integral part of synthetic biology" (Spec. 1:11–12). Existing methods for assembling synthetic DNA oligonucleotides into longer constructs "utilize a combination of polymerase or ligase enzymes to join shorter oligonucleotides (e.g., molecules that are 50 to 200 nucleotides in length) to form constructs that are as long as 1,000 to 5,000 base-pairs" (*id.* at 1:13–18).

The Specification discloses methods for assembling sets of oligonucleotides to produce a synthon by enzymatically assembling the oligonucleotides in a defined order (*id.* at 14:1–3). "Sequence assembly can be done using a variety of different methods, including, but not limited to polymerase chain assembly . . . and ordered ligation" (*id.* at 10:13–16). Sets of oligonucleotides include the same terminal indexer sequence, which locates the set to a discrete feature on an addressable array (*id.* at 14:13–20). Figure 1, partially reproduced below, illustrates the step of locating the sets.

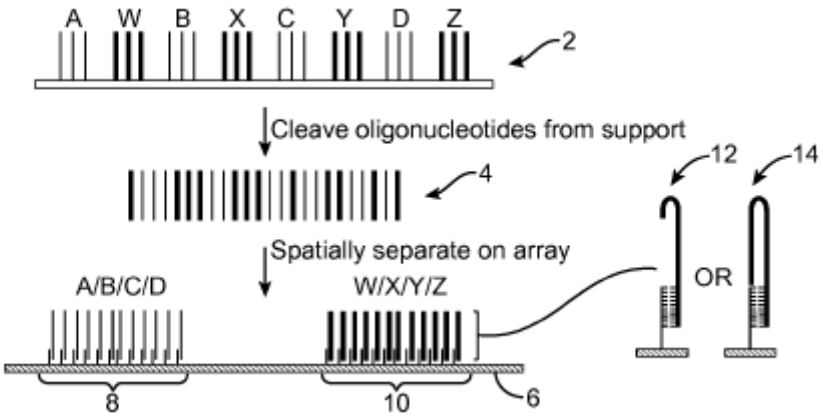

Figure 1 illustrates oligonucleotide set A, B, C, and D located to feature 8 and oligonucleotide set W, X, Y, and Z located to feature 10 (*id.* at 14:19–22).

After locating the sets, the method includes the step of contacting the array with a solution to produce discrete droplets encapsulating the features (*id.* at 15:1–4). The droplet solution contains all the necessary reagents to assemble the hybridized oligonucleotides into a synthon (*id.* at 15:3–11).

The Claims

Claims 1–8 and 12–16 are on appeal.[3] Independent claim 1 is representative and reads as follows:

> 1. A method comprising:
>
> (a) obtaining a mixture of multiple sets of oligonucleotides,
>
> wherein each set of oligonucleotides comprises at least two different assembly sequences,
>
> wherein the oligonucleotides within each set each comprise a terminal indexer sequence and each set can be assembled to produce a synthon,
>
> wherein the oligonucleotides within each set of oligonucleotides have the same terminal indexer sequence, and each set of oligonucleotides has a different terminal indexer sequence;
>
> (b) hybridizing the terminal indexer sequences of the oligonucleotides in the oligonucleotide mixture to a planar array, thereby spatially-separating the different sets of oligonucleotides from one another;
>
> (c) contacting the planar array with a solution, thereby producing an array of discrete droplets, wherein each droplet comprises one or more features of the planar array;
>
> (d) placing an immiscible liquid over the droplets, thereby producing an array of discrete reaction chambers that are each defined by a droplet; and
>
> (e) after step (d) incubating the planar array under conditions by which synthons are assembled in the discrete reaction chambers, while the droplets are on the planar array.

[3] Claims 9–11 and 17–20 are cancelled. Appeal Br. 15–16.

The Issues

A. The Examiner rejected claims 1–3, 6, and 12–16 under 35 U.S.C. § 103 as obvious over Jacobson[4] and Myerson[5] (Ans. 4–12).

B. The Examiner rejected claims 4 and 5 under 35 U.S.C. § 103 as obvious over Jacobson, Myerson, and Baynes[6] (Ans. 12–14).

C. The Examiner rejected claims 7 and 8 under 35 U.S.C. § 103 as obvious over Jacobson, Myerson, and Myllykangas[7] (Ans. 14–16).

A. 35 U.S.C. § 103(a) over Jacobson and Myerson

The Examiner finds Jacobson teaches a method of assembling polynucleotide constructs having predefined sequences on an addressable array (Ans. 4). The Examiner finds Jacobson teaches binding a plurality of oligonucleotides, i.e., a set, to a discrete feature of the array, hydrating the array to form a droplet on the feature, and ligating the oligonucleotides to form a larger nucleotide, i.e., a subassembly (*id.* at 5). The Examiner finds "Jacobson teaches the oligonucleotides comprise a unique primer binding site (i.e.[,] terminal indexer sequence) that is used to selectively amplify a specific subset of oligonucleotides" (*id.* at 6).

The Examiner finds Myerson teaches "different sets of oligonucleotides compris[ing] a unique 5′ barcode sequence (i.e.[,] detection primers) wherein the barcode is the same for each oligonucleotide within an individual set and wherein each set of oligonucleotides comprises a different barcode sequence" (*id.* at 10–11). The Examiner determines it would have

[4] Jacobson et al., US 2012/0220497 A1, published Aug. 30, 2012.
[5] Myerson, US 2010/0113296 A1, published May 6, 2010.
[6] Baynes et al., US 2008/0287320 A1, published Nov. 20, 2008.
[7] Myllykangas et al., US 2012/0157322 A1, published June 21, 2012.

been obvious for one of ordinary skill in the art "to modify the teachings of Jacobson to feature terminal adaptors that facilitate hybridization to a solid support as taught by Myerson . . . result[ing] in the predictable outcome of a method of obtaining oligonucleotides comprising terminal indexer sequences and hybridizing these oligonucleotides to an array" (*id.* at 12).

The issue with respect to the rejection is: Does the evidence of record support the Examiner's findings that Jacobson and Myerson render the claims obvious?

Findings of Fact ("FF")

1. Jacobson teaches "methods and devices for conducting sub-microvolume specified reactions within a droplet" by providing a substrate "comprising a plurality of surface-bound single-stranded oligonucleotides at discrete features" (Jacobson ¶ 11).

2. Jacobson teaches "a set of predefined features may be selectively hydrated, thereby providing hydrated oligonucleotides," which may be "exposed to further processing within a droplet volume" whereby "the droplet acts as a virtual reaction chamber" (Jacobson ¶ 11).

3. Jacobson teaches "[e]ach plurality of oligonucleotides is bound to a discrete feature of the support, and the predefined sequence of each plurality of oligonucleotides attached to the feature is different from the predefined sequence of the plurality of oligonucleotides attached to a different feature" (Jacobson ¶ 13; *see also* Jacobson ¶ 15).

4. Jacobson teaches "the support or array is addressable: the support includes two or more discrete addressable features at a particular predetermined location (i.e., an 'address') on the support. Therefore, each

oligonucleotide molecule of the array is localized to a known and defined location on the support" (Jacobson ¶ 62).

5. Jacobson teaches "features are typically, but need not be, separated by interfeature spaces to ensure that droplets between two adjacent features do not merge" (Jacobson ¶ 62).

6. Jacobson teaches "the reagents in the reaction volumes promote oligonucleotide or polynucleotide assembly . . . the reaction volumes may contain two or more populations of single-stranded oligonucleotides having predefined sequences in solution" (Jacobson ¶ 98).

7. Jacobson teaches that "two different or more oligonucleotides or polynucleotides may be immobilized or synthesized at the same location (or feature) on the solid support thereby facilitating their interaction after amplification within the same droplet" (Jacobson ¶ 118).

8. Jacobson teaches "oligonucleotides in a given droplet may hybridize to each other and may assemble by PCR or ligation" to form a subassembly (Jacobson ¶ 125).

9. Myerson teaches oligonucleotide microarrays having addressable features, where each feature is made up of oligonucleotides bound to a surface of a solid support (Myerson ¶¶ 30, 35).

10. Myerson teaches:

> FIG. 4 illustrates the use of a mixture 51 of three different detection primers, 54, 58 and 59, obtained by the methods such as shown in FIG. 1 and simultaneously labeled such as shown in FIG. 2. Primer 54 comprises barcode$_1$, and target-specific segment$_1$, and 50% of primer 54 has been labeled. Primer 58 comprises barcode$_2$, and target-specific segment$_2$. 25% of primer 58 was labeled. For primer 59, comprising barcode$_3$ and target-specific segment$_3$, 0% was labeled. The mixture 51 of primers is hybridized at step 56 with barcode array 50. The

> features on array 50 comprise "antibarcode" probes that are complementary to the barcode sequences of the respective primers. For example, for antibarcode$_1$, probe sequence 52 is exactly complementary to barcode$_1$. Both of the labeled primers 54 and 54′, as well as the unlabelled primers 54″ and 54‴ are hybridized at feature 66 comprising probe sequence 52. Labeled primer 58, and unlabeled primers 58′, 58″, and 58‴ are hybridized at feature 67. Unlabeled primers 59, 59′, 59″, and 59‴ are hybridized at feature 68.

(Myerson ¶ 95).

Principles of Law

"[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

Analysis

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Ans. 4–12; FF 1–10) and agree that the claims are rendered obvious by Jacobson and Myerson. We address Appellant's arguments below.

Appellant contends "Jacobson does not disclose or suggest discrete droplets comprising sets of oligonucleotides comprising at least two different assembly sequences because the droplets of Jacobson are not discrete" (Appeal Br. 7; *see also* Reply Br. 5–6). Appellant contends that "the droplets of Jacobson must be manipulated, moved and merged in order for desired chemical reactions to occur. In other words, the droplets

described by Jacobson are not discrete droplets and do not form discrete reaction chambers" (*id.* at 7). Appellant further asserts that modifying Jacobson "to exclude manipulating, moving and merging droplets would change the principle operation of its teachings" (Reply Br. 6).

We find this argument unpersuasive for two reasons. First, the Specification expressly states that "[e]ach discrete droplet may occupy a single feature of an array . . . *or* each discrete droplet may occupy multiple features of an array (*where the droplets are actively induced to bleed into each other in a pre-defined way* so that one droplet can contain multiple oligonucleotides)" (Spec. 8:3–8, emphasis added; *see also* Ans. 19). Accordingly, Appellant's Specification expressly defines the discrete droplet to read on Jacobson's embodiments of droplets, which merge into each other in pre-defined way. "When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998).

Second, Jacobson teaches embodiments of merging droplets, as well as "discrete features" that are separated by "interfeature spaces to ensure that droplets between two adjacent features do not merge" (FF 1, 2, 5). Jacobson teaches that each separate droplet may function as a reaction chamber because two or more different oligonucleotides may be immobilized at the same feature on the solid support thereby facilitating their interaction within the same droplet (FF 7). Specifically, Jacobson teaches "oligonucleotides in *a given droplet* may hybridize to each other and may assemble by PCR or ligation" (FF 8, emphasis added). Contrary to Appellant's argument,

choosing one of Jacobson's several embodiments would not change its principle of operation.

Appellant contends that the prior art does not teach multiple sets of oligonucleotides wherein the oligonucleotides within each set have the same terminal indexer sequence but different assembly sequences (*see* Appeal Br. 9–10; *see also* Reply Br. 3). Appellant asserts "Jacobson does not disclose or suggest the claimed sets of oligonucleotides wherein each set has a different terminal indexer sequence" (Reply Br. 3). Appellant asserts "Myerson does not disclose a set of oligonucleotides comprising at least two different assembly sequences wherein the oligonucleotides within each set each comprise a terminal indexer sequence and each set can be assembled to produce a synthon" (*id.* at 4, emphasis omitted).

We do not find this argument persuasive. Appellant argues against the references individually. However, "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Jacobson teaches immobilizing different oligonucleotides having predefined sequences on the same feature and assembling the oligonucleotides into a larger subassembly (FF 6–8). Therefore, Jacobson teaches a set of oligonucleotides comprising at least two different assembly sequences that can be assembled to produce a synthon. Jacobson further teaches "[e]ach plurality of oligonucleotides is bound to a discrete feature of the support, and the predefined sequence of each plurality of oligonucleotides attached to the feature is different from the predefined sequence of the plurality of oligonucleotides attached to a different feature" (FF 3). Therefore, Jacobson teaches that each set of oligonucleotides has a

different pre-defined sequence attached to a different feature. Myerson teaches sets of oligonucleotides characterized by the same barcode or "terminal indexer sequence" (FF 10). Accordingly, the combination of Jacobson and Myerson teaches sets of oligonucleotides having different assembly sequences and the same terminal indexer sequence.

Appellant contends step (b) of claim 1 requires that "the mixture of different sets of oligonucleotides . . . is 'sorted' to different locations on an array by hybridizing the oligonucleotides to an array, where the terminal indexer sequences, which are the same within each set but different from set to set, lead the sets to distinct features on the array" (Reply Br. 4). Appellant asserts that "Jacobson does not teach the mixture of oligonucleotides as claimed, and cannot teach the further sorting of the mixture" (*id.* at 5).

We find that Appellant raises this argument for the first time in the Reply Brief, without explaining why it could not have been raised in the principal brief. *See Ex parte Borden,* 93 USPQ2d 1473, 1477 (BPAI 2010) (informative) ("Properly interpreted, the Rules do not require the Board to take up a belated argument that has not been addressed by the Examiner, absent a showing of good cause.") Nevertheless, the Examiner finds the combination of Jacobson and Myerson teaches step (b) (Ans. 7.) As discussed above, Jacobson teaches contacting a plurality of oligonucleotides having different pre-defined sequences, i.e., a mixture, with an addressable array, thereby binding the oligonucleotides to specific features on the array, i.e., sorting (FF 3). Likewise, Myerson teaches sorting mixtures of oligonucleotides by using barcode sequences to bind the oligonucleotides to specific features on an addressable array (FF 10).

Finally, Appellant contends "Jacobson and Myerson disclose distinct approaches that are directed to solving different problems. These distinct problems and approaches cannot be combined in a meaningful manner to arrive at the claimed technology with any reasonable expectation of success" (Appeal Br. 11). Specifically, Appellant contends "Jacobson describes droplets that must be moved, merged and/ or modified," but Myerson describes detection primers that "remain distinct, immobilized and spatially separated" (*id.*).

We do not find this argument persuasive. As discussed above, Jacobson teaches multiple embodiments, including performing reactions in discrete droplets without moving or merging the droplets. Furthermore, Jacobson teaches using pre-defined sequences to direct oligonucleotides to specific features on addressable arrays (FF 3, 4). Likewise, Myerson teaches using barcode sequences to direct sets of oligonucleotides to specific features on an addressable array (FF 9, 10). "Prior art is analogous if it is from the same field of endeavor or if it is reasonably pertinent to the particular problem the inventor is trying to solve." *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1335 (Fed. Cir. 2015). Contrary to Appellant's argument, Jacobson and Myerson are directed to the same field of endeavor and solve the same problem, i.e., directing oligonucleotides to specific features on an addressable array. Accordingly, using Myerson's barcode sequences to direct Jacobson's oligonucleotides to specific features on the array is a predictable use of the prior art elements according to their establish functions. "Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Conclusion of Law

A preponderance of the evidence of record support the Examiner's conclusion that Jacobson and Myerson render the claims obvious.

B. and C. 35 U.S.C. § 103 over Jacobson, Myerson, and Baynes or Myllykangas

Appellant does not separately argue these obviousness rejections, instead relying upon their arguments to overcome the combination of Jacobson and Myerson (*see* Appeal Br. 12). Having affirmed the obviousness of claims 1–3, 6, and 12–16 for the reasons given above, we also find that further combination with Baynes or Myllykangas renders the rejected claims obvious for the reasons given by the Examiner (*see* Ans. 12–16).

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–3, 6, 12–16	103	Jacobson, Myerson	1–3, 6, 12–16	
4, 5	103	Jacobson, Myerson, Baynes	4, 5	
7, 8	103	Jacobson, Myerson, Myllykangas	7, 8	
Overall Outcome			1–8, 12–16	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED