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Paper No. 46
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NUEVOLUTION A/S,
Petitioner,

v.

CHEMGENE HOLDINGS APS,
Patent Owner.

Case IPR2017-01599
Patent 8,168,381 B2

Before SUSAN L. C. MITCHELL, ROBERT A. POLLOCK, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Claims 1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45
Shown to Be Unpatentable
35 U.S.C. §§ 314, 318(a) and 37 C.F.R. §§ 42.4(a), 42.73

ORDERS
Denying-In-Part Petitioner's Motion to Exclude (Paper 36)
37 C.F.R. § 42.64(c)

I. INTRODUCTION

A. Overview

Nuevolution A/S ("Petitioner") filed a Corrected Petition to institute *inter partes* review of claims 1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45 of U.S. Patent No. 8,168,381 B2 (Ex. 1001, "the '381 patent"). Paper 8 ("Petition" or "Pet."). Chemgene Holdings APS ("Patent Owner") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp."). On January 11, 2018, we instituted trial to review the patentability of claims 1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45 on four of the seven grounds advanced in the Petition. Paper 16 ("Inst. Dec.").

In light of *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), we later instituted trial on the remaining three grounds presented in the Petition ("the additional grounds") and ordered the parties to confer to discuss whether changes to the schedule and/or additional briefing (beyond what was already filed or authorized) were necessary to address the additional grounds. Paper 25. On May 10, 2018, the parties responded via email, informing the Board that no changes to the schedule were necessary, that Patent Owner requested its Preliminary Response (Paper 10) be considered as part of the trial proceedings because Patent Owner intended to rely on its arguments in that paper related to the additional grounds, and that Petitioner requested an enlargement of the word limit for its Reply Brief to Patent Owner Response to address the additional grounds. Paper 26, 2–3. We granted each of those unopposed requests. *Id.* We also granted the parties' request that the Board consider and make part of the trial proceedings the supplemental pre-institution claim construction briefing that was authorized. Paper 14 (Petitioner's Reply to Patent Owner's Preliminary Response) and Paper 15 (Patent Owner's Sur-Reply); Paper 26, 2–3.

During the trial, Patent Owner filed a Response. Paper 22 ("Resp."). Petitioner filed a Reply to Patent Owner's Response. Paper 29 ("Reply"). Patent Owner asked for authorization to file a motion to strike the Reply for alleged non-compliance with 37 C.F.R. § 42.23(b). We did not grant authorization, but permitted the parties to submit supplemental briefing on the issue. Papers 30–32. And, per Patent Owner's request, we authorized argument on that issue at the oral hearing, and we indicated the Board would consider such briefing and oral argument in assessing whether the Reply exceeded the scope permitted under Rule 42.23(b). *Id.* Patent Owner filed a Contingent Motion to Amend (Paper 21), to which Petitioner filed an Opposition (Paper 27).[1] Petitioner also filed a Motion to Exclude Evidence. Paper 36. Patent Owner opposed that motion, and Petitioner replied. Paper 39; Paper 40.

Both parties requested oral argument (Paper 37; Paper 38), which we scheduled for September 18, 2018 (Paper 41). On September 12, Patent Owner submitted an unopposed request to withdraw its Motion to Amend and to withdraw its request for oral argument (Paper 42 (Sept. 12, 2018 Notice of Stipulation and Proposed Order)), which we granted (Paper 43). On September 14, 2018, Patent Owner responded via email to the Board's Order (confirming that the September 18 Oral Argument would proceed (Paper 44)), and stated Patent Owner was ceding its allotted time and had elected not to appear at the Oral Argument. Ex. 3001; Paper 45 ("Tr."), 3:13–18. On September 18, 2018, we held Oral Argument (which Patent

[1] Several days before the scheduled Oral Argument, Patent Owner made an unopposed request to withdraw its Motion to Amend. Paper 42 (Sept. 12, 2018 Notice of Stipulation and Proposed Order). We granted Patent Owner's request. Paper 43.

Owner did not attend) and the transcript has been entered into the record. *See* Tr.

The '381 patent includes two independent claims (and several dependent claims) that recite methods of synthesizing encoded molecules, which are described in detail below. Petitioner's challenges addressed in this Final Written Decision turn in large part on whether the asserted prior art discloses the synthesis of encoded molecules — via the addition of a molecule fragment, a linker, and an oligonucleotide identifier — in the *same* reaction well. Patent Owner agrees this is what independent claims 1 and 5 require, but the prior art discloses only that such molecules are synthesized in multiple *different* reaction wells. *See*, *e.g.*, Prelim. Resp. 3, 8–10, 16–17, 21–26, 45–46; Paper 15, 1, 7; Resp. 11–27, 55–58. Petitioner, on the other hand, argues that a "well" is not limited to any specific physical container or vessel such that the claims embrace synthesis of particular encoded molecules in one container, or in many, if the desired reactions occur and the desired molecules are made. *See*, *e.g.*, Paper 14, 3–4; Reply 1–5. Petitioner alternatively argues that even if the claims require synthesis of particular encoded molecules in the *same* reaction well and this means a single container (e.g., a well on a microtiter plate), this is disclosed in the asserted prior art. *See*, *e.g.*, Pet. 11–13, 36–37; Reply 1, 7–26. We further address the arguments and evidence on these points below.

We have jurisdiction under 35 U.S.C. § 6, and we issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. As explained below, we conclude that Petitioner has established by a preponderance of the evidence in this trial record that claims 1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45 of the '381 patent are unpatentable.

B. Related Proceedings

Petitioner identifies no prior or pending litigation related to infringement or invalidity of the claims of the '381 patent. Pet. 2. Petitioner, however, identifies proceedings in the United States District Court for the Eastern District of Virginia (*Nuevolution A/S v. Pedersen*, No. 1:14-CV-00357 (E.D. Va.)) and the Maritime and Commercial High Court in Denmark (*Nuevolution A/S v. Pedersen*, T-16-12) related to correction of inventorship of the '381 patent and/or Petitioner's entitlement to rights in the '381 patent (or its PCT priority application). *Id*. at 2–3. According to Petitioner, the U.S. district court dismissed the proceedings in Virginia on the basis of *forum non conveniens*. *Id*. at 3.

Patent Owner provides more information about those proceedings. Patent Owner notes that the United States Court of Appeals for the Federal Circuit (*Nuevolution A/S v. Chemgene Holdings APS*, 693 F. App'x 907 (Fed. Cir. July 19, 2017)) affirmed the district court's dismissal. Prelim. Resp. 11 Ex. 2001 (affirming under Fed. Cir. R. 36). Regarding the proceedings in Denmark, Patent Owner asserts that, in February 2016, the "Maritime and Commercial Court ruled that a 2007 Settlement Agreement between Nuevolution and Chemgene completely and perpetually bars Nuevolution from challenging Chemgene's ownership of the PCT application and all related rights, including the '381 patent." Prelim. Resp. 11. Nuevolution, however, appealed this ruling to the Danish Court of Appeal, which remanded the case to the Maritime and Commercial Court on December 8, 2017. *Id.*; Resp. 58.

Petitioner filed another petition for *inter partes* review of claims in U.S. Patent No. 8,168,381 B2 (IPR2017-01598), as well as a petition for *inter partes* review of the sole claim in U.S. Patent No. 8,951,728 B2 ("the

’728 patent” (Ex. 1002)) (IPR2017-01603). Pet. 3–4. The ’728 patent issued from a grandchild application to the ’381 patent. *Id*. at 4; Exs. 1001, 1002.

C. The ’381 Patent

The ’381 patent relates generally to methods for synthesizing encoded molecules. Ex. 1001, 1:19–20. The Specification explains that “[m]ethods are desired for increasing the efficiency of production and screening of chemical libraries with the purpose of generation and isolation of new compounds that can be used for applications in medicine, agriculture and other areas.” *Id*. at 1:27–30.

According to the ’381 patent, known methods for production and screening of chemical libraries include the use of DNA-encoding of compounds. *Id*. at 1:51–2:3. In one approach using “DNA-encoded libraries, each compound in the library is attached to a unique identifier that ‘encodes’ the chemical structure of the molecule to which it is attached.” *Id*. at 1:55–58. DNA-encoding in this way, the Specification explains, provides for efficient screening and selection of compounds with desired characteristics (e.g., binding to a target) because “the isolated compound-DNA complexes can be identified at the end by PCR-amplification, cloning, and sequencing of the DNA portion.” *Id*. at 1:51–55; *see also id*. at 1:27–50. In other words, “the structure of a molecule that is selected in [a] screening assay can easily be decoded by [an] attached unique identifier.” *Id*. at 1:58–60.

As further background, the Specification discloses that DNA-encoded libraries have also been made with a template-based approach. *Id*. at 1:60–63. “In this approach, DNA templates direct the synthesis of the encoded

compounds." *Id*. at 1:62–66. Recovered DNA-compound complexes can be amplified and used in subsequent rounds of synthesis. *Id*. at 1:66–2:3.

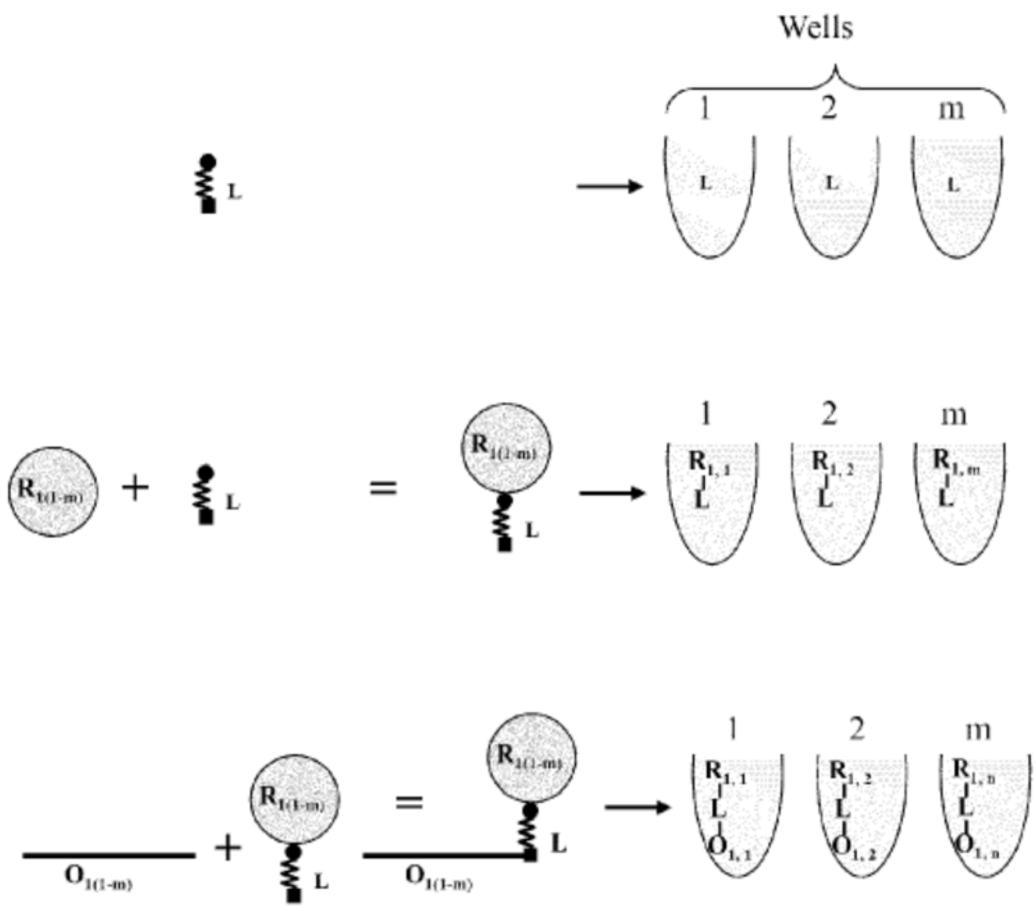
According to the Specification, "[t]he present invention combines the non-templated technique . . . with the template technique . . . and thereby provides an improved method for the generation of oligonucleotide-encoded libraries." *Id*. at 2:6–9; *see also id*. Abstract ("The present invention provides a method for combining the advantages of encoded molecule fragments made by split and mix synthesis with the advantages of template directed synthesis of molecules.").

The Specification defines several terms helpful to understanding the invention. *Id*. at 2:66–7:40. These definitions include, *inter alia*:

> Bi-functional molecule means a bi-functional molecule consisting of an encoded molecule (e.g. a low molecular weight organic molecule) and an oligonucleotide (e.g. a single- or double-stranded DNA molecule), where the oligonucleotide sequence uniquely identifies the identity (structure) of the encoded molecule. The encoded molecule and the identifier are physically connected through a linker moiety.

Id. at 2:66–3:6. The term "[c]arrier molecule" (used interchangeably with carrier and bi-functional carrier molecule) "is a bi-functional molecule that is employed in a Stage 2 templated synthesis, and may be generated by e.g. stage 1 [split and mix] synthesis." *Id*. at 3:14–17. The Specification also defines an "[e]ncoded molecule" as "[t]he portion of the bi-functional molecule that is encoded by the oligonucleotide identifier of the bi-functional molecule." *Id*. at 3:28–30. And the term "[i]dentifier" is defined as "[a]n oligonucleotide that encodes (specifies) the identity of the molecule fragment or encoded molecule to which it is attached." *Id*. at 3:37–39.

The Specification's drawings are also helpful in understanding the invention. Figure 1, reproduced in part below, depicts an initial formation of bi-functional molecules as part of a "Stage 1" synthesis. *Id.* at 9:32–38.

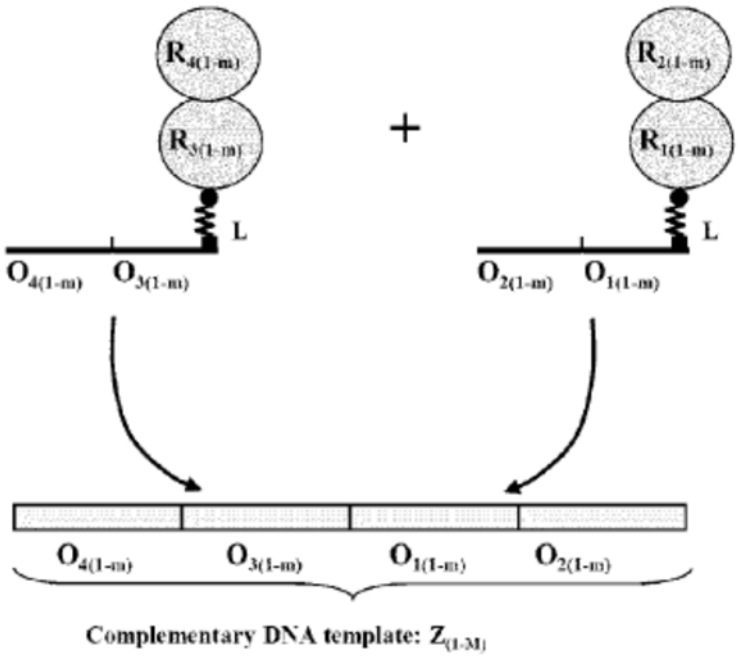


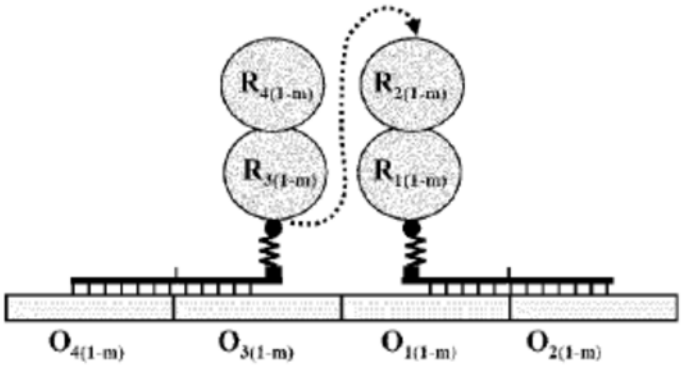
Id. at Fig. 1 (partial). Figure 1 shows a linker molecule "L" is first added to wells (1 through m) in a microtiter plate. *Id.* at 9:44–47. This step is followed by addition of different amino acids (R_1, 1 through m) — "one type of amino acid per well (i.e., a specific amino acid to each well) . . . operatively linked to the linker molecule." *Id.* at 9:45–49. An oligonucleotide identifier (O_1, 1 through m) is then added to each well and operably linked to the linker molecule, such that "[e]ach well now contains a bi-functional molecule that consists of a linker molecule linked to an amino

acid and an identifier oligonucleotide." *Id*. at 9:51–55. In this way, "[t]he sequence of the oligo encodes the type of amino acid added to that well." *Id*. at 9:57–58.

After this initial process, the wells' contents may be pooled and split into wells on a new plate, and a new round of synthesis applied. *Id*. at 9:62–67. For instance, by adding additional amino acids and oligonucleotide identifiers to the new wells, each well will contain a bi-functional molecule consisting of a di-peptide (two amino acids bound to each other) linked to a nucleotide sequence (two oligonucleotide identifiers bound to each other) encoding the di-peptide. *Id*. at 9:63–10:17, Fig. 1.

The Specification also describes and illustrates a "Stage 2" templated synthesis. *See*, *e.g.*, *id*. at 10:51–11:12, Fig. 2. This stage "essentially links together the bi-functional carrier molecules provided by stage 1 in different combinations." *Id*. at 10:54–56. For example, as shown in Figure 2, the method uses a DNA template that is complementary to a pair of bi–functional molecules.





Id. at Fig. 2 (partial). Figure 2 shows that by hybridizing the bi-functional molecules' DNA/oligo portions to a complementary template, the encoded molecules (e.g., di-peptide of each carrier) are brought close and allowed to react — transferring the encoded molecule of one bi-functional molecule to the other. *Id*. at 11:17–26. The reaction shown forms a tetrapeptide that is "linked . . . to a template that encodes the combination of the di-peptides and thus, ultimately encodes the tetrapeptide." *Id*. at 11:27–40.

D. Illustrative Claim

Petitioner challenges claims 1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45 of the '381 patent. Claims 1 and 5 are the challenged independent claims. *See* Paper 9 (Appendix A to Petition, listing claims) 2–3, 5–6.[2] Claim 1 is illustrative and reads as follows:

> 1. A method for synthesizing an encoded molecule comprising the steps of:
>
> a) Adding a linker molecule L to one or more reaction wells;
>
> b) Adding a molecule fragment to each of said reaction wells;
>
> c) Adding an oligonucleotide identifier to each of said reaction wells;

[2] Petitioner's Appendix A (Paper 9) does not include page numbers, but we treat Appendix A as though the pages were consecutively numbered 1–15.

d) Subjecting said wells to conditions sufficient to allow said molecule fragments and said oligonucleotide identifiers to become attached to said linker molecule, or conditions sufficient for said molecule fragments to bind to other molecule fragments and sufficient for said oligonucleotide identifiers to bind to other oligonucleotide identifiers, so as to form bi-functional molecules consisting of an encoded molecule and an oligonucleotide;

e) Combining the contents of said one or more reaction wells, to produce an admixture of said bi-functional molecules;

f) Optionally, distributing the combined product to one or more new reaction wells;

g) Optionally, repeating steps b) to f) one or more times; and

h) Contacting the resulting bifunctional molecule(s) of step e) or g) with one or more templates each capable of hybridizing to at least one of the oligonucleotide identifiers added in step c);

wherein

the linker molecule L contains at least one reactive group capable of reacting with a reactive group in the molecule fragment and at least one reactive group capable of reacting with a reactive group in the oligonucleotide;

the molecule fragments each contain at least one reactive group capable of reacting with a reactive group in the linker molecule L or a reactive group in another molecule fragment, and the reactive groups of each molecule fragment may be the same or different;

the oligonucleotide identifiers each contain at least one reactive group capable of reacting with a reactive group in the linker L or a reactive group in another oligonucleotide identifier, and the reactive groups of each oligonucleotide identifier may be the same or different;

the region of the oligonucleotide identifier added to each well in step c) which hybridizes to said template identifies the molecule fragment added to the same well in step b);

the steps a) to d) may be performed in any order;

the steps b) to d) in step g) may also be performed in any order;

the number of wells in steps a) and f) may be the same or different; and

the oligonucleotide template optionally is associated with a reactive group.

Ex. 1001, 135:34–136:53.

E. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims listed below are unpatentable under 35 U.S.C. §§ 102 and/or 103 based on the following grounds. Pet. 6–7.

Ground	Claims	Reference(s)	Basis
1	1, 3, 5, 6, 10–15, 17, 24–26, 31, 34, 37, 44	Freskgård[3]	§ 102
2	1, 3, 5, 6, 10–15, 17, 24–26, 31, 34, 37, 44	Freskgård	§ 103
3	1, 3, 5, 6, 10–15, 17, 24–26, 31, 34, 37, 44	Freskgård and Pedersen[4]	§ 103
4	1, 3, 5, 6, 10–15, 17, 24–26, 31, 34, 37, 44	Freskgård and Franch '929[5]	§ 103
5	1, 5, 23, 24, 26, 31, 45	Franch '427[6]	§ 102
6	1, 5, 23, 24, 26, 31, 45	Franch '427	§ 103
7	1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, 45	Freskgård and Franch '427	§ 103

[3] Freskgård et al., WO 2004/039825 A2, publ. May 13, 2004 (Ex. 1003).
[4] Pedersen et al., WO 02/103008 A2, publ. Dec. 27, 2002 (Ex. 1004).
[5] Franch et al., WO 2004/024929 A2, publ. Mar. 25, 2004 (Ex. 1005).
[6] Franch et al., WO 2004/083427 A2, publ. Sept. 30, 2004 (Ex. 1016); Petitioner contends that U.S. Application 60/434,439 ("the '439 Application" (Ex. 1017) is incorporated by reference in its entirety into Franch '427. Pet. 100; Prelim. Resp. 50–52; *see* Inst. Dec. 41–43 (analyzing the parties' arguments and concluding the '439 Application is incorporated in its entirety into Franch '427).

Petitioner also relies on, among other evidence, the Declarations of Nicolas Winssinger, Ph.D. Exs. 1015, 1030.

In the initial decision on institution, the Board instituted trial only on those grounds asserting obviousness of the challenged claims over Freskgård (alone or combined with other references) — Grounds 2, 3, 4, and 7 from the table above. Inst. Dec. 47. Nevertheless, after the Supreme Court's decision in *SAS*, we modified the institution decision to include the remaining grounds (grounds 1, 5, and 6) in the trial proceedings. Paper 25.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art would have been one "with a Ph.D. in organic chemistry, molecular biology or a closely related field [, and] with a minimum of 3-5 years of additional experience in drug discovery." Pet. 20; Ex. 1015 ¶¶ 30–32. Patent Owner asserts that the ordinarily skilled person "would have held a doctoral degree in chemistry, molecular biology, or a closely related discipline, and had at least three years of practical academic or industrial laboratory experience." Prelim. Resp. 12.

Although not identical, Petitioner and Patent Owner propose similar qualifications of the skilled artisan. We do not discern a material difference between the parties' proposals and find that the parties' proposals are consistent with the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). We apply Patent Owner's proposal, but our conclusions in this Final Written Decision would be the same under either proposal.

B. Claim Construction

In this *inter partes* review, we interpret claim terms in an unexpired patent based on the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming the broadest reasonable construction standard in *inter partes* review proceedings). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Special definitions must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). We need only construe terms in controversy, and only to the extent necessary to resolve that controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

Upon review of the parties' arguments, including the supplemental pre-institution claim construction briefing that we authorized (Paper 14; Paper 15), we interpreted two claim terms/phrases identified by the parties in our Decision on Institution. Inst. Dec. 21–29. Those terms/phrases are: (i) "template" and (ii) "one or more reaction wells . . . each of said reaction wells." *Id.* The parties do not propose, nor do we discern, that other terms require further construction to resolve the patentability of the challenged claims in this Final Written Decision.

Petitioner proposed an unrebutted interpretation of "template" that we adopted in our Decision on Institution. *Id.* at 28–29. As we explain further below, the parties disputed the interpretation of the phrase "one or more reaction wells . . . each of said reaction wells." *Id.* at 24–28. We interpreted

the term "well" as "a physical containment of reagents, molecule fragments, etc. in a localized space," consistent with the '381 patent's definition of "well." *Id.* at 24–25. Based on, *inter alia*, the "each of said reaction wells" language in claims 1 and 5, we also agreed with Patent Owner and interpreted the entire phrase as requiring that synthesis of any particular bi-functional molecule according to steps (a) to (d) of claim 1 (and steps (a) and (b) of claim 5)[7] be conducted within the *same* reaction well — the *same* physical containment in a localized space. *Id.* at 25–28.

In Patent Owner's view, this interpretation of "one or more reaction wells . . . each of said reaction wells" resolves the challenges raised in the Petition in Patent Owner's favor. *See*, *e.g.*, Prelim. Resp. 3, 8–10, 16–17, 21–26, 45–46; Paper 15, 1, 7; Resp. 11–27, 55–58. That is because, Patent Owner argues, the asserted prior art discloses carrying out the synthesis steps (a) to (c) of claim 1, or steps (a) and (b) in claim 5, in *different* physical containers (e.g., reagent tubes, wells on a microtiter plate, etc.) for each bi-functional molecule. *See*, *e.g.*, Prelim. Resp. 3 ("All of Nuevolution's references synthesize compounds using *different* reaction vessels"). As we explained in the institution decision, however, we were not persuaded that was true for all the prior art references being relied upon by Petitioner and, in particular, we pointed to the cited teachings in Freskgård as also disclosing synthesis of particular bi-functional molecules in the *same* reaction well. Inst. Dec. 30–33, 35–36.

Petitioner embraces the Board's preliminary finding that at least Freskgård teaches synthesis of bi-functional molecules in the same physical

[7] The related language of claim 5 recites "each of m reaction wells . . . each of said m reaction wells." Ex. 1001, 137:43–45.

container (i.e., a well on a microtiter plate) and, thus, in the *same* reaction well. *See*, *e.g.*, Reply 1, 7–21, 26. But Petitioner also urges that a "well" is not limited to any specific number of reaction containers and with a "proper application" of the meaning of "wells," the Board should also reconsider the additional grounds added post-*SAS*. *Id.* at 2–5, 34.

We have considered the evidence and the parties' respective arguments, but we find no reason sufficient to revise our construction of the claim terms in this Final Written Decision. Our claim construction analysis from the Institution Decision, which we apply here, is reproduced in substance below in Sections II.B.1–3. Following that analysis, we address Petitioner's argument in the Reply bearing on claim construction. *See infra* Section II.B.4.

1. The Parties' Pre-Institution Claim Construction Positions

Other than pointing to the definition of "well" in the '381 patent, the Petition did not further address the meaning of "well," and Patent Owner asserted in its Preliminary Response that "no claim term requires express construction." Pet. 20–21; Prelim. Resp. 12. After the filing of the Preliminary Response, however, Petitioner requested briefing on the phrase "each of said reaction wells." Paper 13, 2–3. In particular, Petitioner disputed Patent Owner's assertions that the claims, by reason of the "said reaction wells" language, requires synthesis of at least one bi-functional molecule in the same reaction vessel. *Id*. at 2. We authorized additional briefing from both parties on this issue. Paper 13; Paper 14; Paper 15.

In its additional briefing, Petitioner asserted that the '381 patent's definition of "well" disposes of Patent Owner's arguments. Paper 14, 1–3 (citing Ex. 1002, 4:51–5:4). According to Petitioner, although claims 1 and

5 "may *embrace* bifunctional molecule synthesis in a single container," the claims are "not so limited." *Id*. at 3. Rather, Petitioner argued that "'reaction wells' (as defined and claimed) can be any localized space that allows reaction components (e.g., the claimed linker molecules, molecule fragments, and oligonucleotide identifiers) to react as desired." *Id*. Thus, Petitioner argued, the claims also read on making bi-functional molecules in "more than one container," which "can constitute a 'localized space' (and thus a 'well')" as long as the components for making one type of bi-functional molecule are kept separate from the components used to make other bi-functional molecules. *Id*.

Petitioner cited embodiments in the '381 patent where, Petitioner asserted, more than one container is used to synthesize bi-functional molecules. *See*, *e.g*., *id*. at 4 (citing Example 12 as showing the addition of a linker molecule and oligonucleotide identifiers in several PCR tubes for ligation, followed by transfer of the reaction products to Eppendorf tubes for addition of molecule fragments). Petitioner argued claims 1 and 5 must be interpreted to cover those embodiments, and that Patent Owner's assertions are flawed insofar as they seek to limit the claims to other embodiments in the '381 patent. *Id*. at 4–5. And, Petitioner argued, the claims require neither "compatible conditions," nor prohibit intermediate "purification" or "isolation" steps. *Id*. at 6–7.

Patent Owner, in its additional briefing, argued that Petitioner's interpretation and lexicography argument overlooks the "each of said" language of claims 1 and 5. Paper 15, 1–3. According to Patent Owner, when read in its proper context, "the construction of 'each of said reaction wells' unambiguously means that the synthesis of any particular bifunctional molecule according to steps (a) to (c) [of claim 1] is conducted within the

same reaction well." *Id*. at 2 (emphasis omitted). Patent Owner argued that, the express definition of "well" aside, the interpretation cannot "remov[e] the 'each of said' limitations" that precede the term "well" in the claims. *Id*. at 3–4 ("[N]othing in this definition leads to a construction of 'each of said reaction wells' where reactants for each bifunctional molecule are conveyed to *different* wells for each of steps (a) to (c) . . . ."). Further, Patent Owner asserted, "[s]ome disclosed embodiments fall within the 'each of said reaction wells' limitations, while others do not." *Id*. at 5–6.

2. "one or more reaction wells . . . each of said reaction wells"

According to the Specification, the term "well" "defines a physical containment of reagents, molecule fragments, etc. in a localized space." Ex. 1001, 4:51–53; *see also* Pet. 21. The Specification explains that a "well" may comprise, *inter alia*, the well of a microtiter plate, any container, a reagent tube, or a bead to which the reagents and molecules to be kept separated are attached. Ex. 1001, 4:53–57. This separation, while not necessarily absolute, "should preferably ensure that the major components of a given well are the desired components." *Id*. at 4:58–61. As a further example, the Specification explains that a "nanocompartment" where hybridization of oligonucleotide strands holds reactive groups of bi-functional molecules in proximity to each other may also be considered a "well." *Id*. at 4:61–5:4.

"[I]f the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or

prosecution history,"[8] we will accord the claim term that specified definition. *See CCS Fitness, Inc. v. Brunswick Corp*. 288 F.3d 1359, 1366 (Fed. Cir. 2002); *see also Paulsen*, 30 F.3d at 1480 ("Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision."). We interpret the term "well" in the manner defined by the '381 patent. It means "a physical containment of reagents, molecule fragments, etc. in a localized space." Ex. 1001, 4:51–53. And, as the Specification explains, it may be a well on a microtiter plate, a reagent tube, or the like, or even a nanocompartment where the desired components are physically contained in a localized space for a reaction to take place. *Id*. at 4:53–5:4.

But the definition of "well" alone does not resolve the claim construction dispute here. Steps (b) and (c) of claim 1 use the phrase "*each of said* reaction wells," and step (b) of claim 5 uses the phrase "*each of said* m reaction wells," thus referring back to the "one or more reaction wells" in step (a) of claim 1 and the "each of m reaction wells" in step (a) of claim 5. *Id*. at 135:38–41 (claim 1), 137:41–48 (claim 5) (emphases added).

We give effect to all claim terminology, including the "each of said" language preceding "reaction wells" in steps (b) and (c) of claim 1 and step (b) of claim 5. *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so."). The claim term "said" signals that there is antecedent basis in the claim for the "said"

[8] The parties do not identify any relevant portions of the prosecution history specific to interpretation of the "each of said reaction wells" and "each of said m reaction wells" phrases in claims 1 and 5.

claim term. *See* MPEP § 2173.05(e). We agree with Patent Owner that the limitation "one or more reaction wells . . . each of said reaction wells" means that the synthesis of any particular bi-functional molecule according to steps (a) to (c) of claim 1 is conducted within the *same* reaction well because "said" indicates that the reaction wells of steps (b) and (c) are the same respective reaction wells as in step (a). Paper 15, 2. Similarly, we agree with Patent Owner that the "each of m reaction wells . . . each of said m reaction wells of claim 5" means that the synthesis step (b) in claim 5 for any particular bi-functional molecule takes place in the same respective reaction well as claim 5's step (a). *Id.*

This interpretation is reinforced by claim 1's further requirement that "the region of the oligonucleotide identifier added to each well in step c) . . . identifies the molecule fragment added to *the same well* in step b)." Ex. 1001, 136:41–44 (emphasis added); *see also id.* at 138:22–24 (stating in claim 5 "the oligonucleotide identifier added to each well in step b) and e) identifies the molecule fragment added to the *same* well in the respective step") (emphasis added). Accordingly, whether the reaction well of steps (a) – (c) (and (d)) of claim 1, or the reaction well of claim 5's steps (a) and (b), wherein a particular bi-functional molecule is synthesized by a linker becoming attached to a respective molecule fragment and oligonucleotide identifier is, for example, a tube or a nanocompartment in that tube, it must be the *same* reaction well — the *same* physical containment and localized space. By contrast, a process where the linker and oligonucleotide are attached in a PCR tube, followed by transfer of the reaction products to an Eppendorf tube where attachment of the molecule fragment and linker occurs, involves *different* reaction wells. And we are unpersuaded claims 1 and 5 encompass such synthesis in different reaction wells.

We recognize, but are not persuaded by, Petitioner's contention that Patent Owner's reading of claims 1 and 5 is too narrow because it does not cover all the '381 patent's preferred embodiments. Paper 14, 4. As Patent Owner points out, "[t]he fact that one construction may cover more embodiments than another does not categorically render that construction reasonable." Paper 15, 5–6 (quoting *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 747, 755 (Fed. Cir. 2016)). Further, as confirmed by the Federal Circuit, "the claims of the patent need not encompass all disclosed embodiments." *TIP Systems, LLC. V. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008) (citing *PSN Ill., LLC v. Ivoclar Vivadent, Inc.*, 525 F.3d 1159, 1167 (Fed. Cir. 2008)). That is particularly true when, as here, "to construe the claim term to encompass the alternative embodiment[s] . . . would contradict the language of the claims," i.e., "each of said reaction wells" and "each of said m reaction wells." *Id.*

Petitioner does, however, persuade us that claims 1 and 5 do not include any "compatible conditions" requirement, or exclude an intermediate "isolation" or "purification" step in carrying out steps (a)–(c) of claim 1 or steps (a) and (b) of claim 5. Paper 14, 6–7. Claims 1 and 5 are open-ended and use the transitional phrase "comprising" to introduce those steps. Also, the Specification and the claims indicate that those steps "may be performed in any order." *See*, *e.g.*, Ex. 1001, 2:50, 8:62, 136:46, 138:25–26. Thus, applying to claim 1 for instance, the linker could be added first (step (a)), followed by the oligonucleotide identifier (step (c)), with the two becoming attached as recited in step (d). Nothing in this sequence precludes purifying the intermediate reaction product, with the proviso that the step of adding the

molecule fragment (step (b)), when taken, must occur in the *same* well as steps (a) and (c) of claim 1.

3. "template"

Petitioner proposed an interpretation for the term "template." Pet. 21–22. That term appears in two limitations of claim 1: in step (h), which recites "[c]ontacting the resulting bifunctional molecule(s) of step e) or g) with one or more templates each capable of hybridizing to at least one of the oligonucleotide identifiers added in step c)" and in one of the wherein clauses reciting "the region of the oligonucleotide identifier added to each well in step c) which hybridizes to said template identifies the molecule fragment added to the same well in step b)." Ex. 1001, 135:57–60, 136:42–45. The terms "template" and "templates" also appear in steps recited in claim 5. *Id.* at 137:62–67, 138:1–6.

Petitioner asserted that, under the broadest reasonable interpretation consistent with the Specification, "a POSA would understand the term 'template' to be 'an entity capable of binding carrier molecule(s) to bring molecule fragment(s) into reactive proximity with another reactive group.'" Pet. 22 (quoting Ex. 1015 ¶¶ 91–95). Further, according to Petitioner, the reactive group can be on the template or another carrier molecule. Pet. 22.

The term "template" is not expressly defined in the '381 patent. In support of Petitioner's proposed interpretation, as "an entity capable of binding carrier molecule(s) to bring molecule fragment(s) into reactive proximity with another reactive group," Petitioner cited disclosures from the Specification further explaining the term. Pet. 21–22; *see*, *e.g.*, Ex. 1001, 8:4–8, 10:59–64, 70:3–8, Fig. 4. Petitioner also cited extrinsic evidence (Dr. Winssinger's testimony) explaining how the ordinarily skilled person

would understand the term "template" as used in the patent and claims. Ex. 1015 ¶¶ 91–95. We find that the cited evidence is consistent with Petitioner's proposal. During trial, Patent Owner did not challenge Petitioner's proposal or explain why it is incorrect. Prelim. Resp. 12. Accordingly, consistent with our Decision on Institution, we interpret "template" as "an entity capable of binding carrier molecule(s) to bring molecule(s) into reactive proximity with another reactive group." Inst. Dec. 28–29.

4. Petitioner's Claim Construction Argument In Reply — "one or more reaction wells . . . each of said reaction wells"

Petitioner argues that, although it "advances no new theory" in its Reply, it further explains that the term "well" is defined by two functions: "*containment*" and "*separation*." Reply 1, 3. These are not structural, Petitioner argues, and so long as the functions are maintained during carrier synthesis to obtain the molecules one desires, the "said reaction wells" limitation is met. Reply 5.[9] Here again, Petitioner argues that the type or

[9] Patent Owner argues the Board should exclude Petitioner's Reply under Rule 42.23(b) because "Petitioner did not raise the current 'functional' claim construction arguments" in the Petition or in its seven pages of additional claim construction briefing. Paper 32, 1. The claim construction issue was already thoroughly briefed pre-institution. Papers 13, 14, 15. Petitioner's argument in Reply that a "well" should be interpreted with a focus on function, not structure is a slight twist on Petitioner's earlier arguments, but the thrust of Petitioner's argument is still largely the same. *Compare* Paper 14 *with* Reply, 1–3. Accordingly, rigid application of Rule 42.23(b) to exclude the Reply is not justified on this record. And, in any event, Petitioner's functional interpretation is unpersuasive for reasons already explained. The Reply also invokes certain claim construction opinions on the "said reaction wells" phrase provided for the first time in Dr. Winssinger's second declaration. Ex. 1030 ¶¶ 5–12. This extrinsic evidence is both untimely and insufficient to persuade us that claims 1 or 5 carry a

number of physical reaction vessels is irrelevant if the desired reagents are reacted and the desired products obtained. *Id.*; Tr. 9:3–10:22.

We find no persuasive rationale to revise our claim construction of "one or more reaction wells . . . each of said reaction wells" and remain unpersuaded that Petitioner's functional interpretation is correct for the reasons explained above. Also, a well is a physical structure defining a localized space where the synthesis of the encoded molecules takes place. The '381 patent's examples of wells are *physical* structures — a "well of a microtiter plate," a "container," a "reagent tube," etc. Ex. 1001, 4:53–58.[10] The Specification does not identify an exhaustive and closed list of all example structures that might be considered a "well." But that does not convince us that, where multiple physical structures each representing a localized space are used to synthesize a particular encoded molecule (e.g., adding and reacting a linker and molecule fragment in a well on a microtiter plate, and then moving the reaction products to an Eppendorf tube for addition and reaction with an oligonucleotide identifier), that the claimed steps ((a)–(c) as in claim 1, or (a) and (b) in claim 5) occur in the *same* reaction well as required. Petitioner points us to no disclosure in the '381 patent where such a transfer between *different* physical structures for the key synthesis steps is described as taking place in the *same* reaction well.

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meaning that, as explained, is inconsistent with the plain language of the claims in light of the Specification.

[10] Each of the example structures for a "well" listed in the definition section is also identified in a singular, not plural, form. There is no disclosure of a "well" as including wells on a microtiter plate, containers, or reagent tubes, etc. Ex. 1001, 4:51–5:4.

C. Principles of Law

To show anticipation, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). The prior art need not, however, use the same words as the claims in order to find anticipation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). To the contrary, it is permissible to take into account not only the literal teachings of the prior art reference, but also the inferences the skilled artisan would draw from the reference. *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017); *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A claim is unpatentable under 35 U.S.C. § 103 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 to the person of ordinary skill in the art at the time of the invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). "If a person of ordinary skill in the art can implement a predictable variation [of the claimed subject matter from what is taught and suggested in the prior art], § 103 likely bars its patentability." *Id*. at 401. The question of obviousness is resolved on the basis of underlying factual determinations 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 ordinary skill in the art; and (4) objective evidence of obviousness.[11] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the

[11] Neither party submitted evidence of secondary considerations in this case.

prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.*

D. Grounds Based on Freskgård (Grounds 1, 2, 3, 4, 7)

In this Section, we address Petitioner's challenges to the claims as anticipated by, or over obvious over, Freskgård (Grounds 1 and 2). We also address here the challenges based on Freskgård combined with one of Pedersen, Franch '929, or Franch '427 (Grounds 3, 4, and 7, respectively).

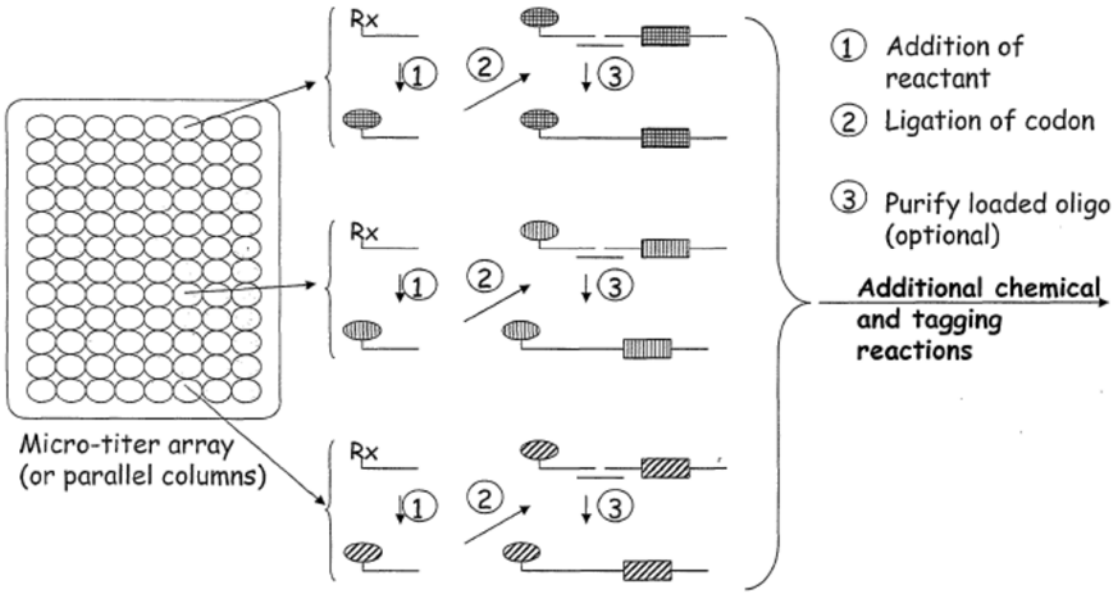
1. Overview of Freskgård

Freskgård "relates to a method for obtaining a bifunctional complex comprising [a] display molecule part and a coding part," as well as "a method for generation of a library of bifunctional complexes." Ex. 1003, 1:10–13. Freskgård teaches these libraries may be formed by so-called "Mode 1" (one-pot synthesis) and "Mode 2" (split-and-mix synthesis) methods, or "advantageous[ly]" through combinations of these methods. *Id.* at 11:18–12:16, 27:12–29, 35:30–36:34.

Freskgård teaches the synthesis of various types of building blocks and bi-functional molecules in the formation of a library of complexes. *See*, *e.g.*, *id.* at 5:29–6:17, 95:5–13, Figs. 1–2, 11–13. According to Freskgård, "[a] functional entity attached to a nucleic acid may be referred to [] as a building block and specifies a chemical entity in which the functional entity is capable of being reacted at the chemical reaction site." *Id.* at 5:32–34. Freskgård discloses "[t]he oligonucleotide of the building block may or may not hold information as to the identity of the functional entity." *Id.* at 6:1–2. Further, in embodiments, the building block comprises an "anti-codon identifying the functional entity." *Id.* at 6:5.

Embodiments for synthesizing bi-functional molecules and libraries of molecules are illustrated in, for example, Figures 11–13 of Freskgård (e.g., Mode 2 or split-and-mix synthesis). Figure 13 is reproduced below.

Fig. 13

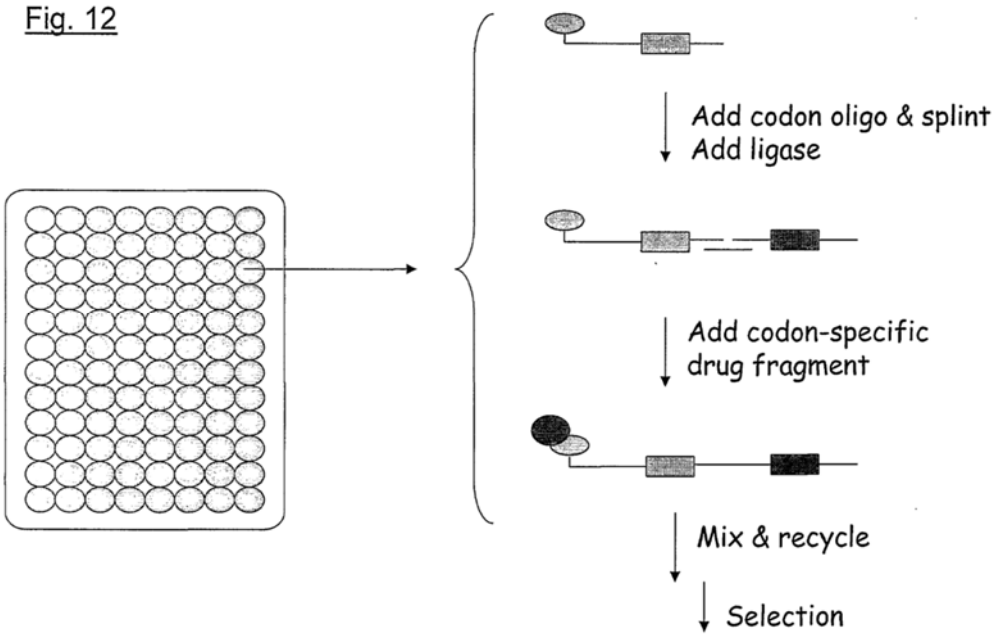


Id. at Fig. 13.[12] Figure 13 shows a 96-well microtiter plate to the left and, to the right, a process for forming bi-functional molecules. *Id*. at 95:5–32. More specifically, Freskgård teaches a reactive group (Rx) attached to an oligonucleotide (horizontal line) is dispensed into the variety of the wells. *Id*. at 95:25–27. Then, "[i]n a first step, the reactive group in each compartment is reacted with a reactant, in a second step a codon oligonucleotide and a splint is added together with a ligase to ligate covalently the codon oligonucleotide to the reacted nascent bifunctional

[12] As we find in the art and as explained by Dr. Winssinger, in depicting bi-functional molecules, particular shading (or hatch marks) is used to show correspondence between the relevant molecule fragments and oligonucleotide/codon identifiers that encode such fragments. *See*, *e.g.*, Ex. 1003, Figs. 12–14; Ex. 1015 ¶¶ 45, 64, 480; Ex. 1004, Fig. 5A.

complex, and in a third step the ligation product is recovered." *Id*. at 27–30. According to Freskgård, "[t]he content of the wells may subsequently be combined and used as a library of bifunctional complexes or recycled for another round of reaction and addition of tag." *Id*. at 95:30–32; *see*, *e.g.*, *id.* at Fig. 14 (showing use of Figure 13's library in further rounds); *see also id*. at Figs. 11–12, 93:11–95:22.

Another embodiment of Freskgård's Mode 2 synthesis is shown below in Figure 12.



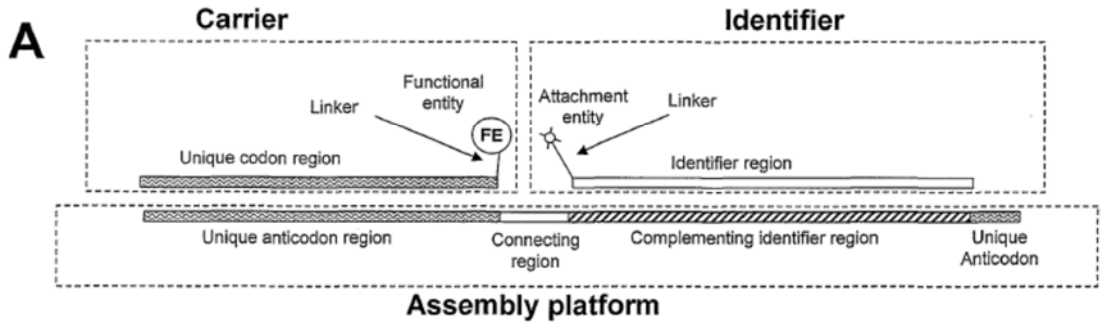
Ex. 1003, Fig. 12. Figure 12 also shows a 96 well microtiter plate, and Freskgård teaches that "[i]n each well or in a selected number of wells, the process to the right occurs." *Id.* at 95:5–7. According to Freskgård, initially a nascent bifunctional molecule or complex is provided that "comprise[s] a chemical reaction site (oval) attached to a codon (rectangle) through a linker (line)." *Id.* at 95:7–8. In the process shown, a codon oligonucleotide (dark rectangle) and drug fragment (dark oval) are reacted and added to the

complex.[13] *Id.* at 95:9–18. Although not shown in Figure 12, in subsequent steps, Freskgård teaches "[t]hen the content of each well is combined and, optionally divided into a range of wells again for a second round of reaction and encoding." *Id.* at 95:20–21; *see*, *e.g.*, *id.* at Fig. 14.

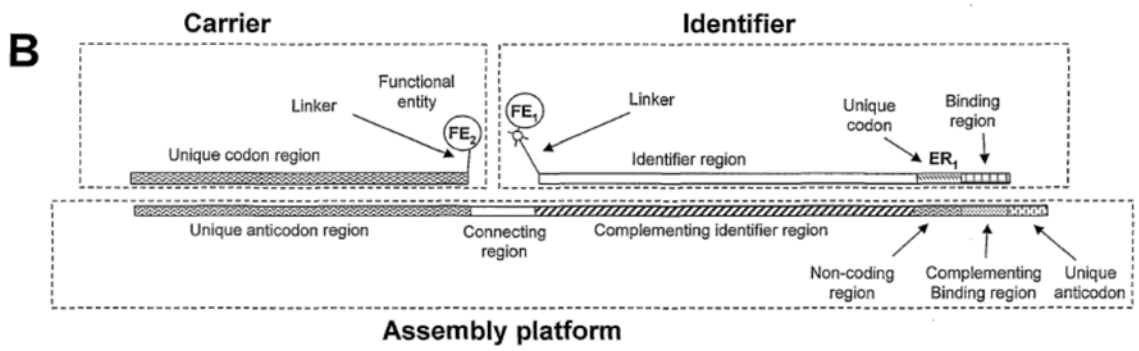
Freskgård discloses further embodiments for forming bi-functional carrier molecules according to a Mode 2 synthesis. *See*, *e.g.*, *id*. at 133:15–140:4 (Example 7), 151:10–154:6 (Example 9).

Freskgård also discloses examples of Mode 1 synthesis including a "three-strand" procedure that employs an "assembly platform" (i.e., template) to which bi-functional carrier molecules may hybridize. *Id*. at Fig. 7, 26:4–16, 92:18–26. This procedure is illustrated in Freskgård's Figure 7 below.

Figure 7.



[13] Freskgård teaches that "Fig. 13 outlines an embodiment with the encoding and reaction step reversed compared to the embodiment shown in Fig. 12." Ex. 1003, 95:24–25. In other words, in Figure 12, the reactant (e.g., codon-specific drug fragment) is added and attached to the reactive group/linker after attachment of a codon-oligonucleotide. *Id*. at Fig. 12, 95:5–22.



Id. at Fig. 7. Figure 7 shows that "[t]he identifier and building block [carrier] can be assembled on an assembly platform," to allow for functional entity transfer from the carrier molecule to the attachment entity of the identifier. *Id*.; *see also id*. at 26:4–16, 92:18–26. Freskgård teaches "[t]he assembly platform [] contains a unique anticodon region with a specific sequence . . . [that] will anneal [i.e., hybridize] to the unique codon region in the carrier." *Id*. at 26:10–13;[14] *see also id*. at 127:23–129:11, 133:16–140:18, 143:4–144:16.

2. Analysis: Anticipation by Freskgård (Ground 1)

Petitioner asserts that claims 1 and 5 are unpatentable under § 102 as anticipated by Freskgård. Pet. 36–73; Reply 7–26, 38. Petitioner also relies on Dr. Winssinger's Declarations. Ex. 1015; Ex. 1030. Petitioner cites substantial evidence and provides argument that each of the steps, and all limitations, in claims 1 and 5 are disclosed in Freskgård. Pet. 10–13, 36–73; Ex. 1015 ¶¶ 409–450; Reply 7–26, 38; Ex. 1030 ¶¶ 16–54. Patent Owner argues that this challenge should be denied because Freskgård does not

[14] Freskgård further teaches "[t]he unique anticodon [on the platform] can either be identical to the unique anticodon region or a shorter or longer sequence . . . [and] [t]he sequence of the unique anticodon can be used to decode the unique anticodon region. This will obtain the unique codon region which codes for the functional entity." *Id*. at 26:18–24.

disclose all the limitations of the challenged claims.[15] Prelim. Resp. 21–27; Resp. 11–35, 41–42, 44–53, 55. We discuss the evidence and the parties' arguments further below.

We begin by addressing the parties' arguments on disputed limitations in claims 1 and 5, and then address Petitioner's argument and our assessment that Freskgård teaches the additional claim limitations that Patent Owner does not specifically dispute are disclosed in Freskgård.

i. "one or more reaction wells . . . each of said reaction wells"

This limitation is relevant, in particular, to steps (a)–(d) of claim 1, and steps (a) and (b) of claim 5, which are part of what Petitioner characterizes as the "carrier synthesis" steps. Pet. 11–12, 18, 36–48. As described above (Section II.B.), a key dispute here is whether the asserted prior art discloses that particular bi-functional (carrier) molecules are synthesized according to the claimed steps in the *same* reaction well.

Patent Owner contends Ground 1 does not account for the "each of said reaction wells" language of claim 1 and the similar language in claim 5. Prelim. Resp. 21–26. Patent Owner initially focuses on the Petition's citation of Examples 2, 7, and 9 of Freskgård as satisfying the so-called "carrier synthesis steps," and Patent Owner argues those examples do not prepare molecules within the same reaction well. *Id*. at 21–26; *see id.* at 26 ("Example 2 therefore uses two separate reactions . . . and two separate

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[15] In its Preliminary Response, Patent Owner also argued that institution on Ground 1 should be denied on a discretionary basis under 35 U.S.C. § 325(d) because Freskgård was before the Examiner during prosecution. Prelim. Resp. 20. We did not exercise our discretion to deny institution on that basis. *See* Inst. Dec. 31–32.

reaction vessels. Furthermore, these separate reactions use different solvents and different pH."); *id.* at 24 ("Example 7 therefore uses four separate reactions separated by isolation steps and four separate reaction vessels, with different solvents and vastly different scales."); *id.* at 23 ("Example 9 therefore uses four separate reactions separated by isolation steps and four separate reaction vessels, with different solvents and different pH."). In short, Patent Owner contends those examples describe *different* reaction wells to prepare particular bi-functional carriers and, thus, do not meet claim 1's and claim 5's requirement for synthesis in the *same* reaction well. *Id*.

As we explained at institution, Patent Owner's argument was persuasive as to Examples 2, 7, and 9 of Freskgård, and we found that Petitioner had not met its burden in showing adequately that *those* examples describe performing steps (a)–(d) of claim 1 or steps (a) and (b) of claim 5 in the *same* reaction well. Inst. Dec. 31–34. But Freskgård's teachings — and Petitioner's challenge — are not based solely on Examples 2, 7, and 9. To the contrary, Petitioner also repeatedly identifies, *inter alia*, Figures 12 and 13 (and descriptions related to those Figures) as evidencing a disclosure of the relevant carrier synthesis steps. Pet. 11–13, 36–38, 41, 46, 48 ("Carrier synthesis is also generally disclosed in Figures 11-13. (*See also*, Ex. 1003, 93:11–94:8, 95:5-32.)"; *see also*, *e.g.*, Ex. 1015 ¶¶ 412–414, 426–429.

We find Figures 12 and 13 of Freskgård show a 96-well microtiter plate to the left, and illustrate the synthesis of a particular bi-functional molecule (or molecules) by combining a linker, molecule fragment, and oligonucleotide identifier (e.g., fragment-specific codon) in individual wells to the right. Ex. 1003, Figs. 12–13, 95:5–32. In describing Figure 12, Freskgård discloses that "[i]n each well or in a selected number of wells, the

process to the right [combining and reacting the linker, etc.] occurs." *Id*. at 95:5–6; Ex. 1015 ¶¶ 412–414; Ex. 1030 ¶¶ 31–32; *see supra* Section II.D.1.

As to Freskgård's Figures 12 and 13, Patent Owner raises several arguments during trial. Resp. 11–35 (regarding claim 1), 44–53 (similar arguments regarding claim 5). First, Patent Owner argues Petitioner gave an insufficient explanation of how those figures satisfied the claimed steps and that Petitioner's misunderstanding that the claims required synthesis in the same reaction well is fatal to Petitioner's challenge. *Id.* at 14–22. Second, Patent Owner argues Petitioner's expert admitted Figures 12 and 13 do not disclose conducting reactions within the same reaction well, and, Patent Owner contends, those figures depict multi-container reactions. *Id.* at 12–14, 22–27. And third, Patent Owner contends, Figures 12 and 13 do not disclose adding the "linker" as claimed. *Id.* at 27–35. We address these arguments in turn.

We do not agree with Patent Owner's first argument, related to Petitioner's alleged misunderstanding of the claims and defects in the explanations in the Petition. Patent Owner made this argument before, which we considered and tacitly rejected when we instituted trial on various Freskgård-based grounds. *See* Paper 15, 7 (Patent Owner argued Petitioner's failure to "take the elementary step of addressing the 'each of said [reaction wells]' claim limitations . . . is fatal to Nuevolution's Petition."). Nor does Petitioner's alleged misunderstanding of claims 1 and 5 *exclude* the claim interpretation applied by Patent Owner, which interpretation the Board adopted and applies in this Final Written Decision. As explained above, Petitioner has consistently argued that the claims encompass synthesis of particular bi-functional carrier molecules in a single container, or many. *See*, *e.g.*, Paper 14, *passim*.

Neither does the Petition's focus on Examples 2, 7, and 9 versus Figures 12 and 13 of Freskgård demonstrate that the Petition is fatally defective. It is true, as Patent Owner argues, that much of the Petition's analysis and explanation is devoted to Freskgård's Examples 2, 7, and 9. *See*, *e.g.*, Resp. 14–18.[16] But prior art is generally read and considered in its entirety for all that it discloses. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983); *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (holding "the prior art as a whole must be considered"). And here, Petitioner explicitly and repeatedly cites Freskgård's Figures 12 and 13, it provides snapshots of Figure 13, which the Petition describes as an illustrative embodiment of Mode 2 (carrier) synthesis, and Petitioner points to Figures 12 and 13 (and the accompanying disclosures related to those figures) as another teaching beyond the cited examples for satisfying the carrier synthesis steps claimed ((a)–(d) in claim 1 and (a)–(b) in claim 5). *See* Pet. 36–38, 41, 46, 48; *see also* Pet. 74–75 (reiterating reliance on Figs.

[16] In Reply, Petitioner asks the Board to revisit Examples 7 and 9 because, Petitioner argues, some of the four separate reactions described for those examples are not germane to the claimed steps (asserting that the first reaction relates to linker preparation and the fourth reaction is a deprotection step occurring after admixture). Reply 21–26. According to Petitioner, Freskgård does not affirmatively disclose that the key reactions (the second and third) in these examples require transfer to a new vessel. *Id.* This is a close call when other embodiments described in Freskgård (*see*, *e.g.*, Ex. 1003, 95:5–32, and Figs. 12–13) are considered; but we remain unpersuaded that those examples (7 and 9 (or Example 2)) specifically describe synthesis of particular molecules in the same reaction well as claimed. *See* Resp. 14 (citing, e.g., Ex. 2005 (Winssinger Tr.), 185:4–9, 187:7–188:11 (declining to "fit" Example 9 into Fig. 12)); *but see id.* at 184:4–185:2 (testifying that Example 9 is connected to Fig. 11, and that Figs. 12–14 are more specific examples of the synthesis described in Fig. 11).

11–14 and the related descriptions of those figures from Freskgård as showing the carrier synthesis steps recited in claims 1 and 5 for the § 103 challenge); *see also*, *e.g.*, Ex. 1015 ¶¶ 410–423, 426–429.[17] That those citations or explanations may have included less detail as compared to what the Petition provides for Examples 2, 7, and 9 of Freskgård does not demonstrate that the Petition itself was defective in identifying a disclosure in the prior art of bi-functional molecule synthesis in the same reaction well as claimed. Indeed the Board, citing relevant teachings in Freskgård and where those teachings were identified in the Petition, understood sufficiently this basis of Petitioner's challenge. Inst. Dec. 31–34. Without putting form over substance, we did not and cannot ignore the cited disclosures related to Figures 12 and 13, a plain reading of which suggests synthesizing particular bi-functional molecules in the same reaction well on a microtiter plate, simply because they were not emphasized to the same degree as other cited disclosures of Freskgård. The dispositive issue now is whether, by a preponderance of the evidence developed through trial, the Petition and the

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[17] Patent Owner contends that, in describing Figure 13, "the petition asserts that the process shown in Figure 13 is conducted in 'different wells.'" Resp. 34. That contention is somewhat misleading. The Petition, at the portion Patent Owner cites, states that Figure 13 "illustrates a Mode 2 embodiment where different carrier molecules are prepared in different wells, by attaching different molecule fragments ('reactants') and single-stranded oligonucleotide identifies ('codons') to a linker molecule." Pet. 36–37. The term "different" as used there relates to preparation of several different bi-functional molecules with different molecule fragments, etc., each in different wells of the microtiter plate. Indeed, Figure 13 depicts preparation of at least three different bi-functional molecules on the plate. "Different," in that context, does not mean that several different wells were used or needed for making any *particular* bi-functional molecule (e.g., any one of the three shown).

Board's Institution Decision is correct that Freskgård does disclose the relevant synthesis steps in the same reaction well. *Genzyme Therapeutic Prods. L.P. v. Biomarin Pharma. Inc.*, 825 F.3d 1360, 1367 (Fed. Cir. 2016) ("The purpose of the trial in an *inter partes* review proceeding is to give the parties an opportunity to build a record by introducing evidence—not simply to weigh evidence of which the Board is already aware.").

We also do not agree with Patent Owner's second argument that Freskgård does not disclose conducting reactions within the same reaction well. Patent Owner contends that Dr. Winssinger "admitted that Figures 12 and 13 do not disclose conducting reactions within the same reaction well." *See* Resp. 12–13. According to Patent Owner, "Dr. Winssinger is correct that the figures do not specify whether the depicted reactions are conducted in the same or different physical containers." *Id.* (citing, e.g., Ex. 2005 (Winssinger Tr. 165:3–5 and 174:20–22 (relating to Figures 12 and 13 being a "high level schematic representation."))). Patent Owner further cites Dr. Winssinger's testimony that the chemistry shown in "Figure 12 . . . is not restricted to a particular container format." Resp. 13 (citing Ex. 2005, 196:5–9) (Patent Owner's emphasis).

We have reviewed Patent Owner's arguments and Dr. Winssinger's testimony, but we find the alleged admissions are consistent with Dr. Winssinger's (and Petitioner's) position that Freskgård's bi-functional carrier molecules can be synthesized in a single reaction well or in many wells. Critically lacking in Patent Owner's cited questioning of Dr. Winssinger is whether the skilled person, reading Figures 12 and 13 *and the accompanying disclosures specifically related to those figures*, would have understood Freskgård as disclosing synthesis of particular bi-functional molecules in a single reaction well on a microtiter plate. As Petitioner

points out in response, "PO attempts to spin Dr. Winssinger's testimony" but "the fact remains that Figure 12 'schematically shows a 96 well microtiter plate to the left[, where] **[i]n** each well or **in** a selected number of wells, the process to the right occurs[.]'" Reply 19 (quoting Ex. 1003, 95:5–6) (brackets and emphasis added by Petitioner)). Indeed, Dr. Winssinger makes clear that, when the accompanying descriptions to Figures 12 and 13 are considered, "Freskgård explicitly provides that the processes shown on the right of these figures [the synthesis of the bi-functional molecules] occur *within* individual microtiter wells." *See*, *e.g.*, Ex. 1030 ¶ 36 (citing Ex. 1003, Fig. 12, 95:5–6); *see also* Ex. 1030 ¶¶ 33–34 (Dr. Winssinger explaining how Patent Owner cited his testimony out of context).

Dr. Winssinger also testified that Freskgård "teaches all permutations," including that reactions of the linker, molecule fragment, and oligonucleotide "can all happen *simultaneously*; hence, in the same microtiter." Ex. 2005, 222:7–21 (emphasis added); *see also* Ex. 2005, 211:17–22 ("If the whole process happens simultaneously within a microtiter plate, this would be . . . the simplest example where it happens in the 'said well.'"). As Dr. Winssinger's testimony makes clear, "Freskgård's Mode 2 synthesis may proceed according to a one-step protocol (simultaneous reaction of reactants and tags in the same compartment), and various multi-step protocols (a tagging reaction prior to or subsequent to a reactant reaction in the same compartment)." Ex. 1030 ¶¶ 19–20; *see id.* ¶¶ 22–23. And, as Petitioner points out, this is consistent with Freskgård's express teachings that the reaction events may occur "simultaneously," thus reinforcing that Freskgård does teach synthesis of particular bi-functional molecules in the *same* reaction well. Reply 10–11; *see*, *e.g.*, Ex. 1003, 95:1–3 ("[T]he general principle for split-and-mix [Mode 2] is disclosed, in which

the reaction of the small molecule fragment and the chemical reaction site occurs prior to the encoding step. Obviously, the events can occur in the reverse order or *simultaneously*.") (emphasis added).

Patent Owner further asserts that Freskgård's Figures 12 and 13 do not disclose synthesis in the same reaction well because those figures "contain arrows with the arrowheads pointing *away* from the wells of the microtiter plate." Resp. 22. According to Patent Owner, when arrowheads point away from the plate, this commonly "indicate[s] that contents are removed from the well." *Id.* at 22–27 (citing Exs. 2007, 2008); *see also* Resp. 48–49 (making substantially the same argument for claim 5).

We do not agree that this is always so, especially in light of express disclosure in the record to the contrary. First, as discussed above, Patent Owner's argument is inconsistent with what Freskgård teaches — that the reactions shown to the right (as indicated by the arrows pointing to the right) may *occur in each well*. Ex. 1003, 95:5–6. With respect to Figures 12 and 13 (and related Figure 14), when the contents of the wells are combined or dispensed into separate wells, Freskgård expressly states so. *Id.* at 95:20–22, 95:34–96:2.[18] On this record, figures and descriptions in other references

[18] Patent Owner asserts that Freskgård's Figure 14 uses an arrow pointing toward the microtiter plate, consistent with common use, to show materials added to the wells. Resp. 24–25. Patent Owner is correct inasmuch as Figure 14 shows and Freskgård describes adding the reaction products from Figure 13 to a new microtiter plate, for subsequent rounds of synthesis (addition of further codon-specific drug fragments and codon oligos). Ex. 1003, Fig. 14, 95:34–96:12 ("Initially, the combined contents of the wells from the embodiment of Fig. 13 are dispensed in separate wells."). But that does not mean the subsequent addition of further fragments and codon oligos (as shown by right-facing arrows in Figure 14) requires a removal from that plate or the wells therein. We find that a more reasonable

(Exs. 2007 and 2008) that post-date Freskgård by several years do not persuade us that Freskgård does not mean what it says.[19] Second, Dr. Winssinger testifies that the arrows shown in these more-recent references do not reflect "any common practice in the art" that would contradict Freskgård's explicit teachings made years earlier. Ex. 1030 ¶¶ 34–37. And third, against Freskgård's explicit teachings and Dr. Winssinger's testimony on the same, Patent Owner provides no countervailing testimony or other sufficiently persuasive evidence to demonstrate that a skilled artisan would interpret Freskgård's Figures 12 and 13 (and the related disclosures) consistent with Patent Owner's arguments.

Patent Owner's third argument, regarding the absence of a linker molecule in Freskgård's cited disclosures, is also unavailing. Resp. 27–35; *see also id.* at 50–53. The Petition explains, for example, that Figure 13 and the related disclosure describe attachment of a molecule fragment ("reactant") and a single-stranded oligonucleotide identifier ("codon") to a linker molecule. *See*, *e.g.*, Pet. 36–37, 40, 45, 48; Ex. 1003, Fig. 13, 95:24–32; *see also id.* at Figs. 11–12, 93:11–94:8, 95:5–22. In this context, it is reasonably clear that Petitioner was relying on, for example, Figure 13's "nascent bifunctional complex," which comprises a reactive group (Rx) and oligonucleotide portion as satisfying the claimed "linker" in step (a) of the

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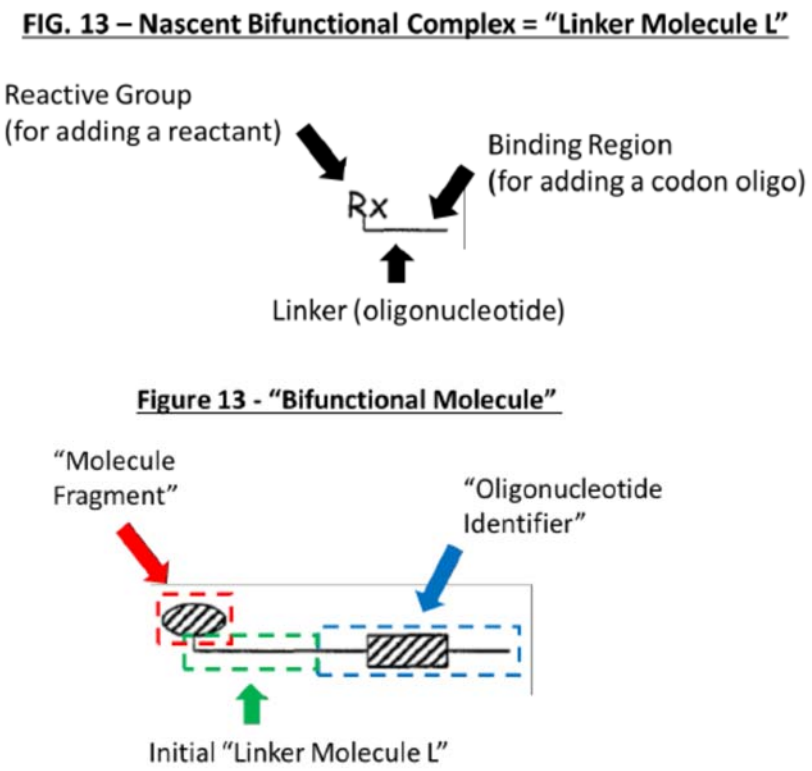
interpretation, consistent with the description for related Figures 12 and 13, is that the right-facing arrows identify the chemical reactions occurring within the individual wells of the plate in this subsequent synthesis round.

[19] Petitioner argues that Exhibits 2007 and 2008 should be excluded as irrelevant, for lacking probative value, and as hearsay. Paper 36, 5–9. We discuss this argument below (Section III) when addressing Petitioner's Motion to Exclude.

claim. Ex. 1003, Fig. 13, 95:24–32; Inst. Dec. 32–34.[20] As disclosed in Freskgård, this "nascent bifunctional complex" is added to wells on the microtiter plate and subsequently reacted "in each compartment [i.e., well]" with a reactant and a codon oligo that is specific to the reactant. Ex. 1003, Fig. 13, 95:24–32.

Petitioner also responded to Patent Owner, marking up portions of Freskgård's figures to illustrate more clearly Petitioner's positions on the claimed "linker." Reproduced below are mark-ups of Fig. 13:



[20] Similarly, we understood from a plain reading of Freskgård and the Petition that Petitioner was pointing to the initial bi-functional molecule in Figure 12 as representing a linker to which subsequent drug fragments and drug-specific codon oligos are attached — thus forming an encoded molecule specific for that drug fragment. Ex. 1003, 95:5–22, Fig. 12. The analysis provided in this section for the nascent bi-functional complex in Figure 13 applies similarly to the initial bi-functional molecule in Figure 12.

Reply 14–18; *see also* Ex. 1030 ¶¶ 28–31, 42–43. In the annotations above, Petitioner highlights the linker, as well as the molecule fragment and oligo identifier for a representative bi-functional molecule depicted in Freskgård's Figure 13. Patent Owner argues we should exclude Petitioner's Reply for including new argument about, *inter alia*, Figure 13. Paper 32, 2–3.[21] On this record, however, we do not agree that providing a further annotation of a drawing that was repeatedly relied upon in the Petition for the same claim limitations addressed in the Reply is impermissible new evidence or argument. To the contrary, Petitioner's annotations are consistent with the Board's understanding of Petitioner's challenge and the Institution Decision, and they are directly responsive to Patent Owner's contentions that a "linker" is missing in Freskgård's disclosures, including in Figure 13. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1080–82 (Fed. Cir. 2015) (holding that rebuttal evidence may be appropriate when needed to explain, repel, counteract, or disprove an adversary's evidence); *see also Anacor*

[21] Petitioner also provided in Reply a further annotated version of Figure 11 from Freskgård as illustrating bi-functional molecule synthesis in the same reaction well. Reply 8–11. The Petition itself repeatedly cited Figure 11 and the related description in Freskgård as showing carrier synthesis steps like claimed. *See*, *e.g.*, Pet. 11–12, 36, 40, 48. Petitioner's further annotation to Figure 11 and citation to Freskgård's related descriptions about Figure 11 does, on balance, indicate that synthesis for particular molecules may occur in one or many reaction wells. Ex. 1003, Fig. 11, 93:11–95:3 (describing, for example, that addition of a small molecule fragment and a tag encoding for the small molecule to a nascent bi-functional molecule may occur in any order or simultaneously). We conclude that Petitioner's further argument and annotations to Figure 11 are fairly responsive to Patent Owner's arguments related to an alleged absence of a disclosure in Freskgård of synthesis in the same reaction well as claimed, and that exclusion of the Reply is not justified. Paper 32, 2–3; 37 C.F.R. § 42.23(b).

Pharm., Inc. v. Iancu, 889 F.3d 1372, 1380–81 (Fed. Cir. 2018) (holding that an IPR petitioner "may introduce new evidence after the petition stage" in some circumstances such as documenting knowledge skilled artisans would bring in interpreting the prior art); *see also* 37 C.F.R. § 42.23(b) (stating "reply may only respond to arguments raised in the corresponding . . . patent owner response").[22]

Patent Owner argues that a "bifunctional molecule" and a "linker molecule" are not the same thing. Resp. 29–32. Patent Owner notes that the '381 patent provides different definitions for those terms and that different claim provisions relate to the linker and bifunctional molecules. *Id.* Patent Owner's argument is unavailing. The "Linker L" is broadly defined in the '381 patent as an entity with reactive groups adapted for reacting, respectively, with a molecule fragment and an oligonucleotide fragment. Ex. 1001, 4:7–11. Patent Owner does not persuade us that a linker molecule excludes a nascent bi-functional complex (like described in Freskgård's Figure 13), which itself includes reactive groups for attaching to a reactant (molecule fragment) and for ligation to an oligonucleotide fragment. Ex. 1003, Fig. 13, 95:24–32; Reply 15–19; Ex. 1030 ¶¶ 41–42; Tr. 26:3–28:14. Moreover, as Petitioner points out, the '381 patent cites Freskgård as describing an "enablement" of a stage 1 synthesis according to the invention, which "enablement" starts with a "nascent bifunctional complex" similar to Freskgård's Figure 13. Reply 18–19; Ex. 1001, 30:29–42 (describing a

[22] Although we disagree that the further annotations to Freskgård's Figures 11, 12, and 13 are "new evidence," we note that Patent Owner never requested a sur-reply and declined to participate in the Oral Hearing where we had granted Patent Owner the opportunity to provide further argument on the merits and Rule 42.23(b) issues. Paper 30; *supra* Section I.A.

stage 1 process using "[a] nascent bi-functional complex comprising a reactive group [for addition of molecule fragments] and a priming site for enzymatic addition of an oligonucleotide identifier . . . ."). This disclosure in the '381 patent, Petitioner contends, therefore uses a nascent bi-functional complex as a linker molecule. Reply 18–19. On this record, we agree with Petitioner that a "nascent bifunctional complex," such as depicted and described in Freskgård related to Figure 13, qualifies as the linker molecule L in step (a) of claims 1 and 5.

We find that Petitioner has shown by a preponderance of the evidence on this trial record that Freskgård discloses the so-called carrier synthesis steps — steps (a) through (d) of claim 1, and steps (a) and (b) of claim 5. This includes, for the reasons explained above, a disclosure of the limitation "one or more reaction wells . . . each of said reaction wells" because Freskgård discloses that particular encoded molecules may be synthesized in the *same* reaction well. Also, as discussed above, we find that the cited disclosures meet step (a) of claim 1 because, *inter alia*, a "linker molecule L" as claimed encompasses, at minimum, Freskgård's nascent bi-functional complexes such as shown in Freskgård's Figure 13 to which particular molecule fragments and codon oligos are reacted and attached in individual wells of a microtiter plate. Ex. 1003, Figs. 12–13, 95:5–32; Ex. 1030 ¶¶ 19–32, 39–42.

ii. "template" / the "region" limitation

Claim 1 recites, in a wherein clause, that "the region of the oligonucleotide identifier added to each well in step c) which hybridizes to said template identifies the molecule fragment added to the same well in step b)." Ex. 1001, 136:41–44. This limitation relates to claim 1's prior

"[c]ontacting" step (step (h)) where earlier formed bi-functional/carrier molecules are contacted with one or more templates capable of hybridizing to at least one of the oligonucleotide identifiers added in step (c). *Id.* at 135:57–60.[23]

Petitioner contends that Freskgård discloses template-based synthesis of encoded molecules, including in examples that combine Mode 2 carrier synthesis with Mode 1 templated synthesis. *See* Pet. 52–58; Ex. 1015 ¶¶ 443–447. Petitioner contends Freskgård discloses "template-encoded synthesis," such as described in Freskgård's Figure 7A. Pet. 52; *see supra* Section II.D.1. According to Petitioner, Figure 7A, for example, describes a "Mode 1 procedure that employs template 'assembly platforms' having 'unique anti-codon regions' for hybridization with unique carrier molecules." Pet. 52; Ex. 1003, 26:4–27:10, 92:18–26, 92:32–93:9. As Petitioner explains, "[t]he unique anticodon region is said to be 'sequence specific to anneal to the unique codon region in the carrier . . . .'" Pet. 52–53; Ex. 1003, 26:10–13; *see also* Ex. 1015 ¶ 108, 419, 443–445. And, according to Petitioner, Freskgård discloses that this contacting and hybridization of carrier molecules with the template/assembly platform brings carrier molecule fragments (e.g., FE_1, FE_2, etc. like shown in Figure 7) into reactive proximity with an attachment entity or another reactive group of a previously transferred molecule fragment for a further transfer

[23] Claim 5 also includes a "contacting" step (step (h)), where resulting bi-functional molecules are contacted with one or more templates, and in a subsequent wherein clause, claim 5 recites "the oligonucleotide identifier added to each well in step b) and e) identifies the molecule fragment added to the same well in the respective step." Ex. 1001, 137:62–67, 138:22–24. Claim 5, thus, does not recite a "region" limitation.

reaction. Pet. 53–54; Ex. 1015 ¶ 444; Ex. 1003, Fig. 7B, 92:23–26. Because the carrier's unique codon region identifying a molecule fragment hybridizes with the unique anticodon region on the platform/template, Petitioner contends "this method employs also **templates** that **hybridize** with **identifiers ($O_{1,m}$)** in a **region that identifies . . . the fragment ($R_{1,m}$) added to the same well** according to the region limitation." Pet. 54; Ex. 1015 ¶¶ 419, 443–445.

Patent Owner responds that Petitioner does not establish a teaching of "the region limitation" in Freskgård. Resp. 41–42. Patent Owner contends "the petition does not demonstrate or explain how Exhibit 1003 (Freskgård) discloses or suggests an oligonucleotide identifier that hybridizes to a template in a manner that 'identifies the molecule fragment added to the same well in step b), as required by claim 1." *Id.*[24] Insofar as Patent Owner's argument presumes Petitioner's challenge is limited to synthesis of carrier molecules in Freskgård's Examples 7 and 9 (or Example 2) alone, Patent Owner's argument interprets the challenge too narrowly. As explained above, we find that Freskgård discloses in other relied-upon teachings the synthesis of carrier molecules in the *same* reaction well. *See supra* Section II.D.2.i.

Furthermore, by combining Mode 2 carrier synthesis (e.g., like shown in Figure 13) with a Mode 1 (one-pot/template) synthesis, such as shown in

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[24] Patent Owner also argues that, even if Freskgård discloses the "region" limitation, the petition does not articulate a motivation to combine the processes in Figures 12 and 13 with the portions of Freskgård allegedly disclosing the region limitation. Resp. 42. We address this contention below related to Ground 2 (obviousness based on Freskgård), where Patent Owner similarly argues there is no motivation to combine Freskgård's Mode 1 and Mode 2 techniques. *Id.* at 43–44.

Figure 7 of Freskgård, we find claim 1's "template" and "region" limitations are met. *See* Reply 5–6; Ex. 1015 ¶¶ 107, 419, 443–445; Ex. 1030 ¶¶ 14–15. Based on the evidence and Petitioner's persuasive argument, we find Freskgård suggests template-based methods that employ codon-specific hybridization — complete hybridization between a carrier molecule's unique codon region (which uniquely identifies the carrier's molecule fragment) and a unique anti-codon region on an assembly platform/template, and thus provide for template-encoded synthesis.[25] Pet. 52–54; Ex. 1015 ¶¶ 419, 443–445; *see*, *e.g.*, Ex. 1003, Figs. 7A–7B. As Petitioner also notes, the phrase the "molecule fragment added to the same well in step b)" refers back to the molecule fragment and oligonucleotide identifier added to the "said" (i.e., same) reaction well as in steps (b) and (c), which codon oligonucleotide "implicitly contains a sequence (a 'region') that encodes that molecule fragment." Reply 6, 32–33; Ex. 1015 ¶¶ 79, 107, 108. To the extent that the *entire* codon oligonucleotide of a carrier hybridizes to a template (e.g., in a codon specific manner such as described in Figure 7 of Freskgård), we agree with Petitioner that the "region" limitation of claim 1 is met.[26]

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[25] We agree with Petitioner that the template hybridization in claim 1 is more specific than in claim 5, which lacks any "region" requirement. Pet. 52.

[26] Patent Owner asserts that Petitioner is advancing a new claim construction theory related to the "region" limitation, and therefore the Reply should be excluded. Paper 32, 1–2. We disagree. Petitioner is simply applying the evidence to the express language of that limitation in the claim and responding to Patent Owner's contention that Freskgård is somehow deficient. Reply 5–6; Paper 33, 2–3. If Patent Owner was urging the Board to adopt a different meaning for the "region" limitation, Patent Owner never made that position sufficiently clear. *See* Prelim. Resp. 12 (asserting that no claim terms require express construction).

iii. Additional limitations

Petitioner contends that Freskgård discloses the remaining limitations of claims 1 and 5. For example, the Petition cites teachings in Freskgård meeting the relevant admixture, (optional) repetition, and contacting steps. Pet. 48–52; *see*, *e.g.*, Ex. 1003, Figs. 11–14; *see also* Ex. 1003, 36:26–34, 94:10–20 ("In a second round the mixture of bifunctional molecules is split into compartments again. . . ."), 95:30–96:11 ("The content of the wells [in Figure 13] may subsequently be combined and used as a library of bifunctional complexes or recycled for another round of reaction and addition of tag. . . ."), 128:1–129:11, 143:5–144:9; *see also* Pet. 51–54 (regarding contacting step); Ex. 1003, Figs. 7A–7B, 26:4–27:10, 92:18–26; Ex. 1015 ¶¶ 410, 434–449. As to the first three wherein clauses of claims 1 and 5, which clauses generally require reactive groups on the linker, molecule fragment(s), and oligonucleotide identifier(s), we find based on Petitioner's assertions and evidence that those wherein clauses are provided when the carrier synthesis steps of claims 1 and 5 (addressed above) are carried out to form the claimed carriers/bi-functional molecules. *See* Pet. 22, 40–42, 48; Reply 7–15; *cf.* Ex. 1015 ¶¶ 39, 137–141, 448. As explained above, we find the preponderance of the evidence shows that Freskgård's synthesis of bi-functional molecules, such as described for Figure 13, meets the carrier synthesis steps (a) to (d) of claim 1 and (a) to (b) of claim 5, and therein further meets the related, first three wherein clauses in those claims. Ex. 1003, Figs. 12–13, 95:5–32; Ex. 1030 ¶¶ 19–32, 39–42.

Patent Owner does not address the merits of Petitioner's assertions and the evidence regarding the additional limitations. Having reviewed the evidence in this trial record pertaining to the additional limitations in claims 1 and 5, we are persuaded that those limitations are met by the asserted prior

art, and further adopt Petitioner's arguments and cited evidence in this Final Written Decision. *In re Nuvasive*, 841 F.3d 966, 974 (Fed. Cir. 2016) (explaining that the Board need not make specific findings on claim limitations that Patent Owner does not dispute are disclosed in the prior art). We, thus, find that the preponderance of the evidence establishes that Freskgård discloses the remaining limitations of claims 1 and 5.

The anticipation inquiry is not, however, complete. Even if Freskgård discloses all the limitations in claims 1 and 5, Patent Owner argues Petitioner "relies on a mosaic of numerous unrelated disclosures" in Freskgård, and that this "patchwork anticipation position violates *Net MoneyIN* and fails to demonstrate anticipation." Prelim. Resp. 27–28. We agree with Patent Owner that Petitioner's anticipation assertions rely on numerous embodiments described in Freskgård, not all of which are expressly related to each other.

Although we find that all the limitations of claims 1 and 5 are collectively taught in Freskgård, Petitioner's challenge requires picking from among distinct embodiments and disclosures to get there. This includes the Mode 2 (split-and-mix) synthesis described in, for example, Freskgård's Figure 13 with the Mode 1 (one-pot/three-strand template) synthesis shown in, for example, Figure 7. *See supra* Section II.D.2.i–ii. That Freskgård discloses advantages in combining Mode 1 and Mode 2 synthesis methods does not describe sufficiently the exact arrangement of claims 1 and 5 for purposes of anticipation. Ex. 1003, 35:30–36:34; *Net MoneyIN*, 545 F.3d at 1370–71 ("[I]t is not enough [for anticipation] that the prior art reference . . . includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."); *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) (explaining that anticipation requires the art "clearly and

unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."). On this record, Petitioner has not persuasively identified in Freskgård a single-anticipatory description having all the limitations of claims 1 and 5 arranged as in the claims.

Accordingly, we find Petitioner did not meet its burden to establish, by a preponderance of the evidence, that claims 1 and 5 are unpatentable under § 102 by Freskgård. Because Petitioner did not meet its burden to show that Freskgård anticipates the independent claims, neither did Petitioner show that Freskgård anticipates the challenged dependent claims (claims 3, 6, 10–15, 17, 24–26, 31, 34, 37, and 44).

3. Analysis: Obviousness over Freskgård (Ground 2)

i. Claims 1 and 5

Petitioner asserts that claims 1 and 5 (and several dependent claims) are unpatentable under § 103 as obvious over Freskgård. Pet. 74–83. Petitioner incorporates its analysis of the disclosures of Freskgård related to Ground 1 and the challenged claims. *Id.* at 74. Petitioner also points out that Freskgård teaches that Modes 1 and 2 are advantageously combinable because the Mode 2 (split-and-mix) strategy provides for versatile reactions, and the Mode 1 (one-pot/template) strategy provides for high local concentrations of reactants, providing a motivation for the skilled artisan to have combined those techniques. *See*, *e.g.*, Pet. 75–80; Ex. 1015 ¶¶ 528–529 (explaining that a mode 1 synthesis also provides the advantage of ensuring a "close proximity" and "high local concentration promoting the reaction even for reactants having a relatively low tendency to react") (citing Ex. 1003, 36:28–34); *see also* Ex. 1015 ¶¶ 536–549, 550–554; Reply 32–34.

Patent Owner argues that Freskgård does not disclose all the limitations of claims 1 and 5. Resp. 10–29, 43–53, 56. Patent Owner also contends the Petition fails to demonstrate a motivation to arrive at a process conducted within the same reaction well according to steps (a) to (d) and fails to provide any motivation to modify Figures 12 and 13 to arrive at the process recited in steps (a) to (d) of claim 1. *Id.* at 35–36, 43–44; *see also id.* at 53–54 (making similar argument regarding steps (a) and (b) of claim 5). Patent Owner argues that, even if a motivation existed, the Petition "does not establish that a person of ordinary skill in the art would have had an expectation of success in modifying [Freskgård's] multistep syntheses . . . to be conducted within the same reaction vessel." *Id.* at 37; *see also id.* at 54–55. Further to that point, Patent Owner argues, the processes depicted in Freskgård's Figures 12 and 13 (and other Freskgård disclosures) do not provide "specific experimental instructions or even directions" for carrying out synthesis of particular bi-functional molecules in the same reaction well as claimed. *Id.* at 40.

We find that Petitioner has shown, by a preponderance of the evidence on this record, that claims 1 and 5 would have been obvious over Freskgård. We discuss below.

As explained above regarding Ground 1, we find, based on the preponderance of the evidence on this record, that Freskgård discloses all the limitations of claims 1 and 5. *See supra* Section II.D.1–2. For example, at least Figures 12 and 13 and the related disclosures about those figures in Freskgård teach preparation of distinct bi-functional molecules in the same reaction well, and the satisfaction of steps (a)–(d) of claim 1. *See*, *e.g.*, Ex. 1003, Figs. 11–13, 93:11–94:8, 95:5–32; Pet. 11–13, 36–38, 41, 46, 48;

see also Ex. 1015 ¶¶ 412–414, 424–429; Reply 6–21, 32–34; Ex. 1030 ¶¶ 28–31, 36, 42–43.

Petitioner also demonstrates persuasively that Freskgård discloses "templated" synthesis that satisfies claim 1's "region" limitation, and that Freskgård provides express reasons for combining Mode 1 (template-based) and Mode 2 (split-and-mix) techniques. Pet. 74–82 (citing, e.g., Ex. 1003, Fig. 7, 36:26–34, Ex. 1015 ¶¶ 541–542); Reply 32–34. Indeed, we find Freskgård teaches "it may be advantageous to use a combination of a one-pot synthesis strategy (mode 1) and a split-and-mix strategy (mode 2), because each of mode 1 and mode 2 has its virtues." Ex. 1003, 36:1–7. Such virtues include, *inter alia*, "the possibility of having the reactive groups in close proximity" in Mode 1 and the "versatile reactions" provided with a Mode 2 synthesis. *Id.*; *see also id.* at 36:26–34 ("The intermediate library [formed using split-and-mix] is used for the generation of a final library using a one-pot [template] strategy."). Dr. Winssinger echoes these advantages (and others) in his testimony, including the ability to provide and screen large libraries of encoded molecules by combining the techniques. *See*, *e.g.*, Ex. 1015 ¶¶ 526–535, 536–554.

Patent Owner's arguments about Freskgård not disclosing the limitations of claims 1 and 5 are unpersuasive for the reasons explained above. *Supra* Section II.D.2.i–iii. Patent Owner's argument about picking and choosing between embodiments in Freskgård, although persuasive with respect to anticipation, fails to rebut the challenge based on obviousness. Indeed, "picking and choosing may be entirely proper in the making of a 103, obviousness rejection." *Arkley*, 455 F.2d at 587. And here, Petitioner has identified several evidence-supported reasons that we find explain why the skilled person would have predictably and advantageously combined

Mode 2 and Mode 1 techniques to arrive at the subject matter of the challenged claims. Pet. 75–80; Reply 32–34; *see also*, *e.g.*, Ex. 1003, 36:1–34; Ex. 1015 ¶¶ 526–535 (e.g., describing reasons to use bi-functional carrier molecules in combination with a three-strand assembly (template) platform (like shown in Figure 7)). Patent Owner's argument that there is no sufficient motivation or reasonable expectation of success in combining those techniques (*see*, *e.g.*, Resp. 35–36, 43–44) is inconsistent with at least Freskgård's express teachings and substantial expert testimony in this case, and thus, the preponderance of the evidence on those issues weighs in Petitioner's favor.

Patent Owner argues that Petitioner fails to show a "motivation" to arrive at a process for synthesizing bi-functional molecules in the same reaction well as claimed. Resp. 35–36. But, as Petitioner points out and as the Board has explained above, we find Freskgård expressly teaches such synthesis. Reply 26 ("at least Figures 11-13 . . . specifically teach synthesis in the same reaction well according to claims 1 and 5."); Ex. 1003, Figs. 12–13, 95:5–32. Hence, the motivation comes directly from Freskgård and "[a] POSA would not need to modify them [e.g., the methods shown in Figures 12 and 13] in any way." Reply. 26; Ex. 1030 ¶ 56.[27]

Patent Owner argues that an expectation of success in conducting bi-functional molecule synthesis within the same reaction well is also lacking. Resp. 37–39. Yet that argument is unavailing. We are unpersuaded the

[27] Petitioner also states that motivation to synthesize bi-functional molecules in "a single reaction vessel" comes from "Freskgård's teaching that the 'addition of a[n] [identifier] tag may occur prior to, subsequent to, or simultaneous with the reaction' of a molecule fragment (Ex-1030, ¶57; Ex-1003, 28:14-15 (emphasis added), 95:1-3.)." Reply 26–27.

skilled artisan would lack a *reasonable* expectation of success in carrying out the synthesis of particular bi-functional molecules in individual wells of a microtiter plate when that is precisely what Freskgård instructs may be done. Ex. 1003, Figs. 12–13, 95:5–32; *see also id.* at 95:1–3 (teaching that the synthesis of the components can occur "simultaneously"); Ex. 1030 ¶ 57; Ex. 2005, 211:17–22 ("If the whole process happens simultaneously within a microtiter plate, this would be . . . the simplest example where it happens in the 'said well.'"). Teachings in patents and prior art publications (like Freskgård) are presumed to be enabled for the ordinarily skilled person absent persuasive evidence to the contrary, which Patent Owner does not provide. *See In re Antor Media Corp.*, 689 F.3d 1282, 1287–88 (Fed. Cir. 2012); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

Neither are we persuaded "specific experimental instructions" are required to provide the skilled artisan a reasonable expectation of success in carrying out the reactions Freskgård teaches may be carried out in the same reaction well. Resp. 40. We find that the portions of the '381 patent cited by Patent Owner as describing bi-functional molecule synthesis in the same reaction well include a level of detail comparable to Freskgård's detail related to Figures 12 and 13. Paper 15, 5 (citing Ex. 1001, Fig. 1, Abstract, 2:12–17, 8:23–28, 53:4–8, 59:30–46). This suggests, consistent with Petitioner's argument and evidence of record, that skilled artisans would have known how to carry out the synthesis of bi-functional molecules in individual wells of a microtiter plate (as taught in Freskgård) without detailed instructions. *In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (holding "the Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art

references supports the Board's finding that one skilled in the art would have known how to implement the features of the references."); Reply 10–11; Ex. 1030 ¶ 20; Ex. 1003, 27:15–29. So too, Patent Owner's argument that the skilled artisan would have no expectation of success based on Freskgård rings hollow where the '381 patent itself invokes Freskgård's teachings to provide "enablements" of split-and-mix synthesis according to the invention, and where the '381 patent states that "any embodiment of bi-functional molecule synthesis described in said patent application [Freskgård] is applicable for stage 1 [split-and-mix/carrier] synthesis." Ex. 1001, 30:30–32, 30:58–63; Pet. 11; Reply 13.

For the reasons above, upon consideration of the argument and evidence on this entire trial record, we find that Freskgård teaches or suggests all the limitations of claims 1 and 5, and that the skilled artisan would have had reason to practice the method of those claims with a reasonable expectation of success. Accordingly, we conclude that claims 1 and 5 are unpatentable under § 103 over Freskgård.

ii. Dependent Claims

Patent Owner does not address specifically any additional arguments and evidence provided by Petitioner regarding the obviousness of dependent claims 3, 6, 10–15, 17, 24–26, 31, 34, 37, and 44, which Petitioner challenges would have been obvious over Freskgård. *See* Resp. 55 (arguing only that "[t]he petition fails to establish that independent claims 1 and 5 are obvious over Ex-1003 (Freskgård).").

We have reviewed Petitioner's assertions, the cited art, and Dr. Winssinger's testimony regarding the remaining dependent claims. *See* Pet. 58–73, 83; Ex. 1015 ¶¶ 462–472 (analyzing claims 3 and 6), 473–477

(claim 10), 478–482 (claim 11), 483–487 (claims 12 and 13), 488–493 (claims 14 and 15), 494–501 (claims 17, 24, and 25), 502–506 (claims 26 and 44), 507–509 (claim 31), 510–514 and 517–521 (claim 34), 522–525 (claim 37). Having reviewed and considered Petitioner's argument and evidence supporting its challenge to the dependent claims with which we agree, and noting a lack of any distinct rebuttal from Patent Owner regarding those claims, we find Petitioner has demonstrated by a preponderance of the evidence that claims 3, 6, 10–15, 17, 24–26, 31, 34, 37, and 44 are unpatentable as obvious over Freskgård.

4. Freskgård Combinations (Grounds 3, 4, and 7)

Petitioner also challenges claims 1 and 5 (and several of the dependent claims; *see supra* Section I.E) as obvious over Freskgård in combination with one of Pedersen, Franch '929, or Franch '427. Pet. 83–97, 109–114. We begin with overviews of those prior art references. We then address the challenge to claims 1 and 5 under Grounds 3, 4, and 7 as a group because, for each ground, the Petition similarly relies on Freskgård for teaching the claimed carrier synthesis steps (in addition to other claim limitations) and relies on Pedersen, Franch '929, or Franch '427 for teaching templated synthesis, which templated techniques the Petitioner argues are substitutes to the template-based (Mode 1) synthesis in Freskgård and combinable with split-and-mix (Mode 2) carrier synthesis according to Freskgård's teachings. *See*, *e.g.*, Pet. 89–91 (Freskgård/Pedersen combination). So combined, Petitioner contends, the asserted prior art suggests all the limitations of the claims, including the recited steps of "contacting" the carriers/bi-functional molecules with one or more templates (step (h) in claims 1 and 5), and template-encoded synthesis that satisfies the

related wherein clauses of claims 1 and 5 (i.e., as in claim 1, wherein "the region of the oligonucleotide identifier added to each well in step c) which hybridizes to said template identifies the molecule fragment added to the same well in step b)."). *See*, *e.g.*, *id.*; *see supra* Section II.D.2.ii (discussing the claimed "template" and "region" limitations in further detail).

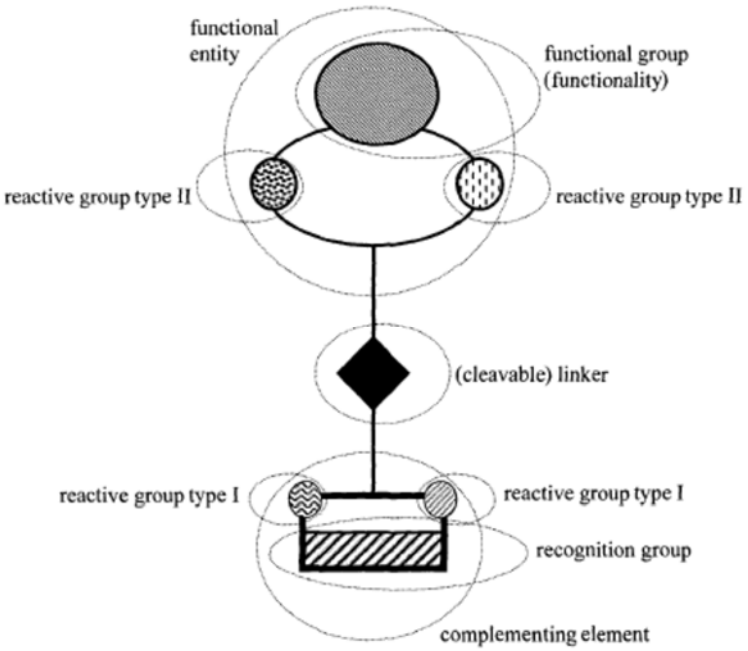
i. Overview of Pedersen

Pedersen relates to "a method for synthesizing templated molecules" that "allows the generation of libraries which can be screened for e.g. therapeutic activity." Ex. 1004, Abstract. Pedersen discloses:

> The templated molecules are preferably synthesized from building blocks comprising a functional entity comprising a functional group and reactive group capable of covalently linking functional groups and forming a templated molecule. The functional entity of a building block is separated from a complementing element by a cleavable linker, or a selectively cleavable linker. The complementing element is capable of complementing a predetermined coding element of the template, thus ensuring a one-to-one relationship between a coding element - or a complementing element - and a functional entity, or a functional group.

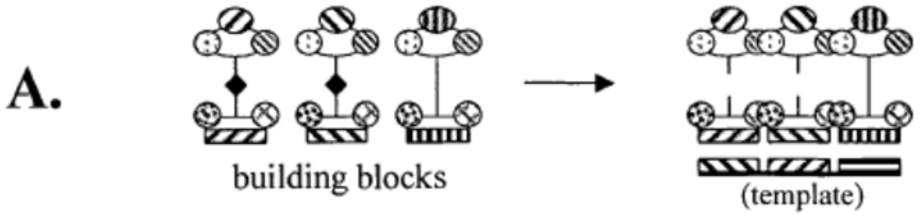
Id. at 13:18–26.

Representative building blocks are shown in Pedersen's drawings. Figure 3, for example, is reproduced below.



Id. at Fig. 3. Figure 3 shows a building block containing a functional entity, a cleavable linker, and a complementing element. *Id*.; *see also id*. at 27:15–25, Fig. 6. Pedersen discloses that "[t]he complementing element contains a recognition group that interacts with a complementary coding element (coding element not shown [in Figure 3])." *Id*. at 27:19–21. An exemplary method of synthesizing building blocks is disclosed in Examples 107 and 108 of Pedersen. *Id*. at 298:13–303:32.

Pedersen also discloses using building blocks in a templated synthesis. *See*, *e.g*., *id*. at 298:13–299:11, 301:1–303:32, Fig. 5A, Fig. 31. Figure 5A, for example, shows a templated synthesis and is reproduced below.



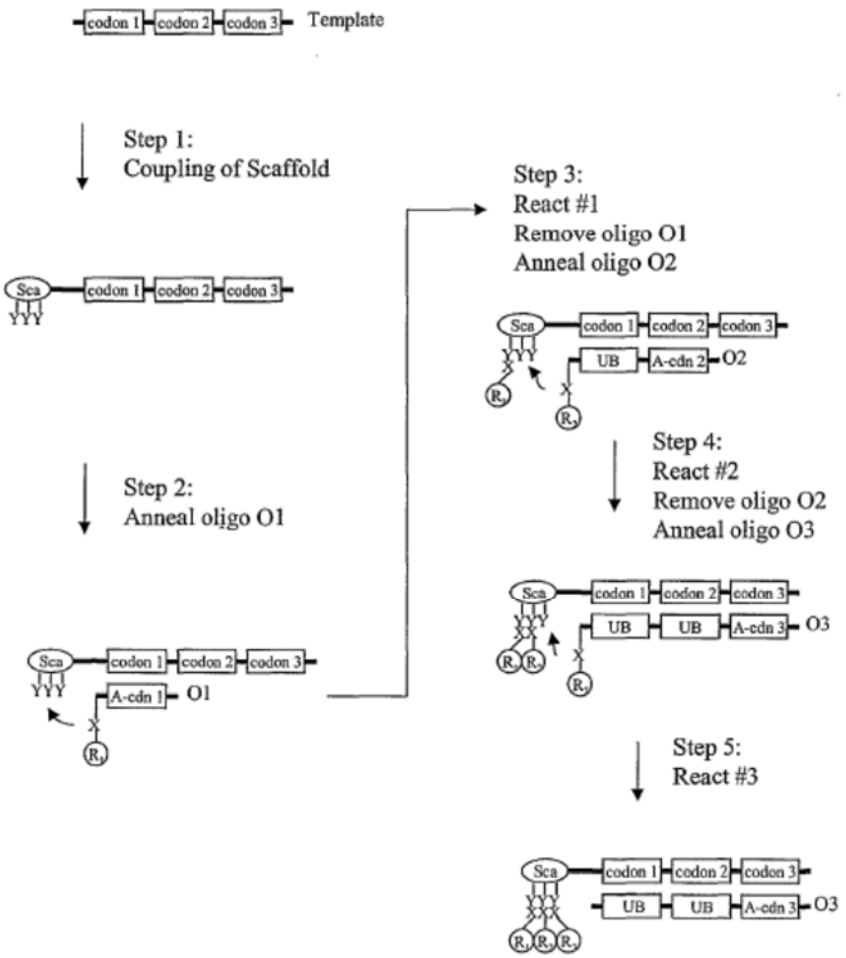
Id. at Fig. 5A. According to Pedersen, Figure 5A shows "[t]hree different complementing elements . . ., each linked to a specific functional entity [such as shown in the building blocks of Figure 3]" and "[t]he right half of the figure includes the template which directs the incorporation of the building blocks by complementary base pairing [i.e., hybridization]." *Id*. at 28:4–9; *see also id*. at 47:23–48:2, Fig. 31, 301:29–303:17.

ii. Overview of Franch '929

Franch '929 relates to "a method for synthesizing a bifunctional complex . . . [that] comprises a template as well as a molecule, the synthesis of which being directed by the template," and the formation of a library of such complexes. Ex. 1005, Abstract. Franch '929 discloses "a template comprising two or more codons in sequence, a first pair of a molecular affinity pair, and a reactive group." *Id*. Further, the method of Franch '929 uses "two or more building blocks, each building block comprises i) an anti-codon capable of recognising a codon of the template, ii) a functional entity comprising at least one reactive group, and iii) a linker connecting the anti-codon and the functional entity." *Id*; *see also id*. at 4:2–26. Franch '929 teaches "contacting the template with a building block under conditions which allow specific hybridisation of the anti-codon of the building block to the codon of the template." *Id*. at 4:16–18.

Figure 1 of Franch '929, reproduced below, is a schematic representation of this hybridization between building blocks and a template.

Fig.1



Id. at Fig. 1. Figure 1 shows, *inter alia*, the step-wise hybridization of building blocks (oligos O1, O2, O3) to a template having a scaffold with reactive groups (Y) for accepting the transfer of molecule fragments (R_1, R_2, R_3) from the respective building blocks. *Id*.; *see also id*. at 52:18–55:2. After the template, which contains three codons, is coupled to a scaffold, "building block O1 is annealed to the template. The building block comprises the anticodon (A-cdn 1) which complements codon 1 of the template." *Id*. at 52:22–27. Then, "the functional entity [R_1] of the first building block is transferred to the scaffold by a direct reaction involving the

reactive groups X and Y." *Id*. at 52:30–32. The process continues similarly for building blocks O2 and O3 as shown. *Id*. at Fig. 1; *see also* Fig. 6.

Examples 1 and 2 of Franch '929 describe the preparation of building blocks, such as used in the process shown above. *Id*. at 72:1–75:32.

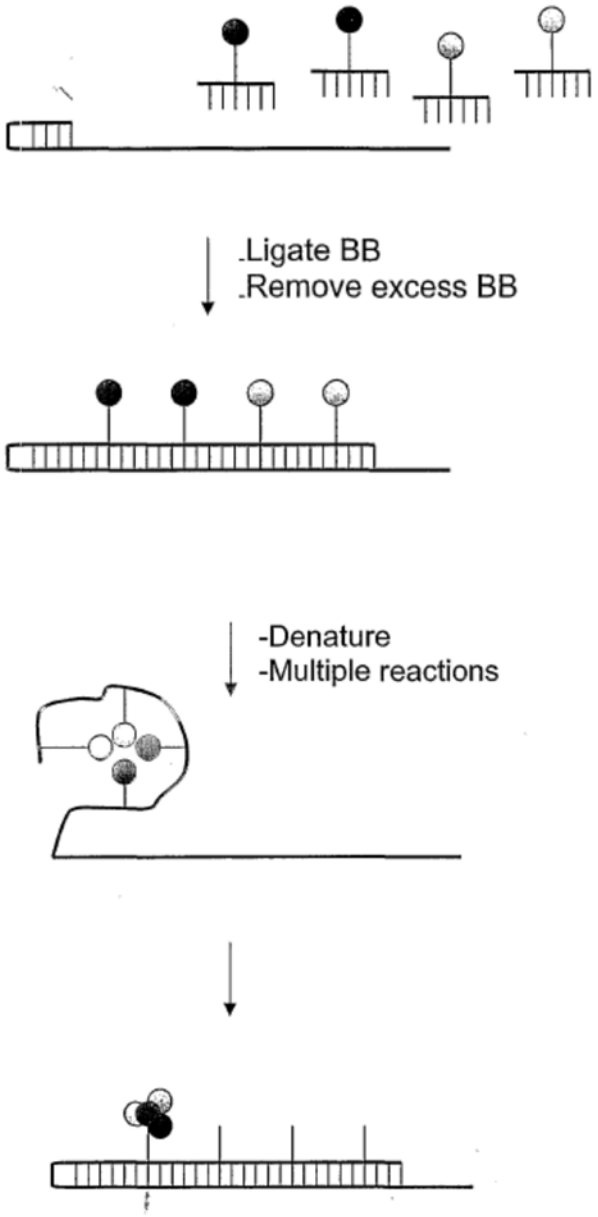
iii. Overview of Franch '427

Franch '427 "relates to a method for synthesizing a bifunctional complex comprising an encoded molecule and an identifier polynucleotide identifying the chemical entities having participated in the synthesis of the encoded molecule." Ex. 1016, Abstract; *see also id*. at 5:8–10.

Franch '427 discloses, *inter alia*, providing "at least one template comprising one or more codons capable of hybridising to an anti-codon, wherein said template is optionally associated with one or more chemical entities," and providing "a plurality of building blocks each comprising an anti-codon associated with one or more chemical entities." *Id*. at 5:14–20. After "hybridising the anti-codon of one or more of the provided building blocks to the template," the anti-codons may be linked and/or the template is linked with the anti-codon of at least one building block, thereby "generating an identifier polynucleotide capable of identifying chemical entities having participated in the synthesis of the encoded molecule." *Id*. at 5:22–28.

An example of this synthesis is shown in Figure 2 of Franch '427, in which multiple building blocks are combined on a template. *Id*. at 67:7–26.

Fig.2



Id. at Fig. 2. As shown in Figure 2, "a template comprising a hairpin loop is provided" and "[v]arious building blocks are added subsequently." *Id*. at 67:13–18. According to Franch '427, "[t]he anticodons [of the building blocks] are designed such that they align[] on the template under

hybridisation conditions," which "is directed by the sequence of the template." *Id*. at 67:18–20. The "anticodons are ligated together," and "the ligation product is made single stranded by inducing denaturing conditions," which then allows the chemical entities to react together and form the reaction product. *Id*. at 67:20–26; *see also id*. at Fig. 2.

Franch '427 provides a more detailed description of the chemical structure of building blocks capable of transferring a chemical entity. *See*, *e.g*., *id*. at 49:9–50:16. Franch '427 discloses that this "building block is the subject of the Danish patent application No. PA 2002 01946 and the US provisional patent application No. 60/434,439 [(Ex. 1017) 'the '439 Application'], the content of which are incorporated herein in their entirety." Ex. 1016, 50:1–4. The '439 Application discloses a method for synthesis of this building block. Ex. 1017, 2:10–19, 16:16–17:28 (Example 3).[28]

iv. Analysis: Obviousness over Freskgård in Combination with Pedersen, Franch '929, or Franch '427

For Ground 3, Petitioner cites and incorporates the argument and cited evidence related to Grounds 1 and 2 (anticipation and obviousness over Freskgård). Pet. 83. Petitioner asserts that Pedersen

> is broadly directed to a one-pot template-encoded synthesis of DNA-encoded chemical libraries, where bi-functional carrier(s) (termed "building blocks") are hybridized with template(s) having coding element(s), such that molecule fragment(s) (termed "functional entities") can react with one another and/or a template reactive group, e.g., an "anchorage point."

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[28] Patent Owner argued pre-institution that the '439 Application was not incorporated into Franch '427. Prelim. Resp. 50–52, 58, 62. We concluded that the '439 Application (Ex. 1017) is incorporated in its entirety into Franch '427 for the reasons explained in the institution decision, which conclusion we maintain and incorporate here. Inst. Dec. 41–43.

Pet. 83–84 (citing, e.g., Ex. 1004, Abstract, Figs. 5, 29–31, 1:5–13, 13:10–26, 44:24–45:8, 45:10–48:2). Petitioner also contends that Pedersen discloses embodiments for synthesizing building blocks for preparing repertoires of such building blocks (carriers) for template-encoded synthesis. Pet. 84; Ex. 1004, 23:16–19; Ex. 1015 ¶¶ 188–209.

Petitioner asserts that the skilled artisan would recognize the similarities between carriers used in Freskgård and Pedersen. Pet. 89. As Petitioner explains, "[i]ndeed, the carrier molecules prepared according to WO '825 [Freskgård], Examples 7 and 9 (and those described in WO '825, FIGS. 11-14) are structurally similar to the WO '008 [Pedersen] carriers." *Id.*; Ex. 1015 ¶¶ 561–562. Thus, Petitioner contends, "a POSA would immediately appreciate that a repertoire of Mode 2 carriers from WO '825 could be utilized for template-encoded synthesis according to WO '008," providing "codon-specific hybridization with the templates from WO '008." Pet. 89–90. According to Petitioner, "this is a simple substitution of one known element . . . for another" — bi-functional molecules/carriers prepared as in Freskgård for the carriers in Pedersen — that would provide predictable results. *Id.*; Ex. 1015 ¶ 561.

Based on the above-noted similarities and the fact that Freskgård "espouses the virtues" of combining Mode 1 and Mode 2 techniques, Petitioner reasons that the skilled artisan "would be especially motivated" to use Freskgård's carriers in Pedersen's template-encoded synthesis methods, thus providing large libraries of template-encoded products. Pet. 90; Ex. 1015 ¶¶ 563, 569; Ex. 1003, 11:22–29, 36:1–14, 36:26–34 (teaching advantages of combining Mode 1 and Mode 2, such as reaction versatility and high local concentrations of reactants). Moreover, Petitioner contends, the skilled artisan "would be motivated to prepare carriers from multiple

rounds of Mode 2 synthesis (e.g., according to WO '825, FIGS. 11-14 or Example 9)" to provide large intermediate carrier libraries for combination with a library of templates as described in Pedersen. *Id.*

Petitioner provides substantially the same analysis for Grounds 4 and 7, but swaps the teachings of Franch '929 and Franch '427 related to template-based reactions for those of Pedersen. *See* Pet. 91–97, 109–112 (explaining that, because of the advantages described in Freskgård of combining Mode 1 and Mode 2 techniques, "the POSA would have applied Mode 2 techniques, e.g., those described in WO '825 Figures 11-13, to prepare carriers for the template-encoded methods according to WO '427, with the expectation that this modification would successfully provide libraries of template-encoded final products"); *see also* Ex. 1015 ¶¶ 574–581, 626–632.

Patent Owner argues that Ground 3 fails because of the same alleged deficiencies of Freskgård asserted above on Grounds 1 and 2. Resp. 55–56. More specifically, Patent Owner contends:

> The Board relied on Exhibit 1003 (Freskgård) for the disclosure of steps (a)-(d) of claim 1 and steps (a)-(b) of claim 5. *See* Paper 16 (Institution Decision) at 37–38. . . . However, for the reasons discussed above regarding Ground 2, the petition fails to establish that Exhibit 1003 (Freskgård) discloses at least steps (a)-(d) of claim 1 and steps (a)-(b) of claim 5. . . . Furthermore, the petition fails to establish that Exhibit 1003 (Freskgård) discloses or suggests other aspects of the claim. . . . Ground 3 does not cure any of the deficiencies of Ground 2.

Resp. 56. Patent Owner makes substantially the same argument for Grounds 4 and 7. *Id.* at 56–58 (arguing Freskgård's alleged deficiencies).

Patent Owner's arguments related to the alleged deficiencies of Freskgård are addressed above (Section II.D.2–3) and are similarly unavailing with respect to Grounds 3, 4, and 7.

We find, based on a preponderance of the evidence on this record, that each of Pedersen, Franch '929, and Franch '427 disclose, among other things, template-directed synthesis methods.[29] When combined with bi-functional molecules synthesized according to Freskgård's Mode 2 (split-and-mix) technique as proposed by Petitioner, we find that the cited references teach all the limitations of claims 1 and 5. *See* Ex. 1003, Figs. 11–14, 95:5–32. We further find that the skilled artisan would have reason to combine the split-and-mix and template-directed techniques to obtain the known advantages of each of those techniques, and that the skilled artisan would have had a reasonable expectation of success in doing so. Ex. 1003, 36:1–14, 36:25–35 (describing combinations of Mode 1 and Mode 2 synthesis and advantages of combining those techniques); Pet. 90, 95, 109; Ex. 1015 ¶¶ 561–565, 574–581, 626–632. And, we also find that the skilled artisan would have had a reasonable expectation of success in carrying out the method claimed, including synthesis of bi-functional molecules in the same reaction well as described in Freskgård, for reasons already explained.

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[29] *See*, *e.g.*, for Pedersen (Ex. 1004, Fig. 5A, 28:4–9, 47:23–48:2, Fig. 31, 301:29–303:17; Pet. 83–90; Ex. 1015 ¶¶ 211–214, 561–565); for Franch '929 (Ex. 1005, Figs. 1, 6; Pet. 91–97; Ex. 1015 ¶¶ 574–581); for Franch '427 (Ex. 1016, Fig. 2, 67:7–26; Pet. 97–102, 109–112; Ex. 1015 ¶¶ 626–632). We further note that, when describing support for "stage 2 synthesis (templated synthesis of bi-functional molecules)," the '381 patent states that "[a]ny embodiment of bi-functional molecule synthesis described in said patent application [Franch '929] is applicable for the stage 2 synthesis of bi-functional molecules." Ex. 1001, 35:4–5, 36:4–7.

Supra Section II.D.3. For the above reasons, we conclude that claims 1 and 5 are unpatentable under § 103 over Freskgård in combination with any of Pedersen (Ground 3), Franch '929 (Ground 4), or Franch '427 (Ground 7).

i. Dependent Claims

Patent Owner does not address specifically any additional arguments and evidence of Petitioner regarding the obviousness of dependent claims challenged under Grounds 3, 4, or 7. *See* Resp. 55–58.

We have reviewed Petitioner's assertions, the cited art, and Dr. Winssinger's testimony regarding the challenged dependent claims. *See* Pet. 58–73, 83–97, 104–106, 109–114; Ex. 1015 ¶¶ 462–472 (analyzing claims 3 and 6), 473–477 (claim 10), 478–482 (claim 11), 483–487 (claims 12 and 13), 488–493 (claims 14 and 15), 494–501 (claims 17, 24, and 25), 502–506 (claims 26 and 44), 507–509 (claim 31), 510–514 and 517–521 (claim 34), 522–525 (claim 37), 602–609 (claims 23, 24, 26, and 45), 610–611 (claim 31). Having reviewed and considered Petitioner's argument and evidence supporting its challenge to the dependent claims with which we agree, and noting Patent Owner's lack of any distinct rebuttal regarding those claims, we find Petitioner has further demonstrated by a preponderance of the evidence on this record the following: claims 3, 6, 10–15, 17, 24–26, 31, 34, 37, and 44 are unpatentable as obvious over Freskgård and Pedersen (Ground 3), as well as over Freskgård and Franch '929 (Ground 4); claims 3, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45 are unpatentable as obvious over Freskgård and Franch '427 (Ground 7).

E. The Additional Grounds (Grounds 5 and 6)[30]

Grounds 5 and 6 (anticipation and obviousness over Franch '427) were added to the trial proceeding following the Supreme Court's decision in *SAS*. Paper 25. Initially, we denied those grounds in the Institution Decision for one key reason. We determined that Petitioner had not met its burden to demonstrate by a reasonable likelihood that the relied-upon prior art (Franch '427, and the '439 Application incorporated by reference into Franch '427) disclosed synthesis of particular encoded molecules in the *same* reaction well as required by claims 1 and 5. *See*, *e.g.*, Inst. Dec. 41–44 ("As Patent Owner persuasively argues (Prelim. Resp. 53–54), Example 3 of the '439 Application [incorporated in Franch '427's disclosure] suggests the reactions of the alleged linker, molecule fragment, and oligonucleotide identifier (together making up a building block) take place in multiple, *different*, reaction vessels, as evidenced by various different reactions and buffers used, and purification and isolation procedures taken."); Pet. 99–101 (relying on Example 3 of the '439 Application (Ex. 1017, 16:16–17:28) as describing the claimed carrier synthesis steps). And, we concluded, the Petition lacked "persuasive argument or a sufficient evidentiary basis to support a finding that Patent Owner's reading of Franch '427 is incorrect." Inst. Dec. 43.

The additional grounds present further bases on which the claims of the '381 patent challenged in this *inter partes* review are alleged to be unpatentable. Inst. Dec. 10, 47.[31] Because we have determined that

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[30] Ground 1 (anticipation by Freskgård) was also added post-*SAS*, but that ground is addressed above in Section II.D.2.

[31] We pointed out that these grounds were largely cumulative, but we did not deny them or the Petition for efficiency purposes because trial was to

Petitioner has shown by a preponderance of the evidence that all of the claims challenged in this Petition for *inter partes* review are unpatentable in light of Grounds 2, 3, 4, and 7, we need not reach the unpatentability of those claims over Grounds 5 or 6. *Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984) (holding that once a dispositive issue is decided, there is no need to decide other potentially dispositive issues); *see*, *e.g.*, *Formlabs Inc. v. Envisiontec, Inc.*, IPR2017-01258 (PTAB Oct. 5, 2018) (Paper 41, 17).

But even turning to Grounds 5 and 6, Petitioner makes essentially three arguments in an attempt to convince the Board to reach a different result than reached in the Institution Decision. First, Petitioner argues that with a change to — or "proper application" of — the meaning of "reaction wells," the Board should revisit whether Franch '427 satisfies the carrier synthesis steps of independent claims 1 and 5. Reply 34–35. Second, Petitioner argues it is not as clear-cut from Franch '427 (as Patent Owner contends) that Franch '427 describes synthesis of encoded molecules in *different* reaction wells. *Id.* Petitioner argues that "[t]here is no mention in Example 3 from Ex-1017 of bifunctional molecule intermediates being transferred to new, or different, reaction vessels after purification" and, instead, Example 3 simply discloses that certain intermediates are redissolved in an MES buffer for further treatment with additional compounds (acetyl fragments). *Id.* at 35. Hence, Petitioner argues, the inference drawn by Patent Owner (on which the Board based its initial determination) is improper. *Id.* And third, for the additional obviousness

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proceed initially only on the Freskgård-based obviousness grounds (Grounds 2–4 and 7). Inst. Dec. 46.

ground (Ground 6), Petitioner argues that even if the cited reactions in Franch '427 are carried out in separate vessels, "a POSA would have nonetheless found it obvious to conduct these reactions sequentially in the same vessel." Reply 37–38.

Petitioner's arguments are unpersuasive and we find, on this record, that the preponderance of the evidence does not demonstrate that claims 1 and 5 are unpatentable based on Grounds 5 and 6. First, we decline to change our claim construction or its "application" for reasons discussed above. *Supra* Section II.B. As explained above, claims 1 and 5 require carrier synthesis steps for a particular bi-functional molecule be conducted in the *same* reaction well, and Petitioner has not demonstrated sufficiently that Franch '427 describes such synthesis. Inst. Dec. 41–44; Prelim. Resp. 50, 52–54, 57–58; Ex. 1017, 16:16–17:28.

As for Petitioner's second argument, even if it might be the case that Franch '427's cited reactions are (or could be) conducted within the same reaction well, such a possibility is inadequate to show that all the limitations are, in fact, disclosed in Franch '427. "Probabilities or possibilities" do not suffice to show that a claim limitation is present. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981, citing *Hansgirg v. Kemmer*, 26 CCPA 937, 940 (1939) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient."). It was Petitioner's burden to make an adequate showing in the Petition on this issue, but we find Petitioner did not do so. Indeed, even during the trial, Petitioner was unable to identify in Franch '427 any adequate disclosure of synthesizing particular carrier molecules according to steps (a)–(c) of claim 1 and steps (a)–(b) of claim 5 in the *same* reaction well as we have construed those steps. Tr. 36:1–19

(discussing Freskgård as providing the only express disclosure of this limitation in the asserted prior art).

Third, Petitioner's assertion that, assuming Franch '427 discloses synthesis of particular carrier molecules in multiple reaction wells, it would have been obvious to modify that process and conduct such synthesis in a single reaction well is a new obviousness rationale provided for the first time in Petitioner's Reply. Petitioner's "*Cf.*" citation to a single paragraph among hundreds in Dr. Winssinger's first declaration does not convince us otherwise. Reply 38 (citing Ex. 1015 ¶ 618).[32] We do not decide in this trial proceeding whether Petitioner's third argument is persuasive or backed with sufficient evidence in Petitioner's Reply. We simply find it goes beyond true rebuttal and is a new rationale for modifying Franch '427 that was not set out adequately in the Petition. Hence, it is not considered here under Rule 42.23(b). 37 C.F.R. § 42.23(b).

III. MOTION TO EXCLUDE

Petitioner moves to exclude five exhibits: Exhibits 2003, 2004, 2006, 2007, and 2008. Paper 36 (Pet. Mot.).

Exhibit 2003 is a press release, Exhibit 2004 is a paper co-authored by Dr. Winssinger, and Exhibit 2006 is a transcript of a conference call between the parties and the Board related to a discovery dispute. Petitioner argues that those exhibits are irrelevant and not cited or relied upon by Patent Owner its briefings. Pet. Mot. 2–5. Patent Owner responds that the exhibits

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[32] Even considering that paragraph from the first declaration, at best, it suggests a possibility for synthesizing particular carriers (such as described in Franch '427) in individual wells, but it does not provide sufficient evidence or persuasive technical reasoning to demonstrate why the skilled person would have been motivated to make such a modification.

are relevant for at least the purpose of maintaining a complete record of Dr. Winssinger's deposition. Paper 39, 1–4.

We do not affirmatively rely on any of Exhibits 2003, 2004, or 2006 in our determinations as part of the Final Written Decision. Patent Owner's Motion to Exclude those exhibits is, thus, dismissed as moot.

Exhibit 2007 is a technical paper authored by Dr. Winssinger and published in CHIMIA in 2013. Ex. 2007. It relates generally to methods for forming encoded molecules by tagging chemical entities with nucleic acids. *Id.* at 340. Exhibit 2008 is a technical paper related to methods for engineering zinc-finger arrays that was published in Nature Protocols in 2009. Ex. 2008, 1471.

Petitioner argues that both Exhibits 2007 and 2008 should be excluded as lacking relevance and because their probative value (if any) is outweighed by the danger of unfair prejudice and likelihood of confusing the issues. Pet. Mot. 6–9. Also, Petitioner argues, both exhibits contain out of court statements that should be excluded as hearsay. *Id.* at 7, 9; *see also* Paper 40, 3–5. Patent Owner responds that Exhibits 2007 and 2008 are relevant and admissible as support for Patent Owner's contention regarding an alleged common practice in the art about the use of arrowheads pointing away from a well to indicate the removal of the contents from the well. Paper 39, 4–8. Patent Owner further contends Exhibits 2007 and 2008 are relevant to rebut Petitioner's evidence about Freskgård's Figures 12 and 13 and whether the arrowheads there indicate the reactions take place in the same or different wells. *Id.* As for hearsay, Patent Owner argues those exhibits are "offered for what [each] teaches, not for the truth of the matter it asserts." *Id.* at 6, 8.

Petitioner's motion is denied with respect to Exhibits 2007 and 2008. Those exhibits are, at minimum, relevant as offered to counter Petitioner's

contentions and impeach Dr. Winssinger's opinions that a skilled person would interpret Freskgård's figures and disclosures as teaching synthesis of encoded molecules in individual wells of a microtiter plate. On this record, the fact that those exhibits post-date Freskgård and the '381 patent's putative priority date by many years goes to their weight, not admissibility. *See also Yeda Research v. Mylan Pharm. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018) (noting that the Board correctly recognized that non-prior art evidence of what was known "cannot be applied, independently, as teachings separately combinable" with other prior art, but "can be relied on for their proper supporting roles," including "how one with ordinary skill in the art would have under-stood a prior art disclosure") (citation omitted). Nor are we persuaded the probative value of those exhibits is substantially outweighed by the risk of unfair prejudice or of confusing the Board. As explained above, we considered those exhibits but simply found them unpersuasive in the face of Freskgård's express teachings and Dr. Winssinger's opinions about Freskgård. *See supra* Section II.D.

Finally, on hearsay, we are unpersuaded that Exhibits 2007 and 2008 qualify as a hearsay statement because they are not being offered for the truth of the matters asserted therein. Fed. R. Evid. 801(c)(2). The exhibits include technical descriptions related to arrows and reactions in wells on a microtiter plate that differ from Freskgård's figures and related descriptions. Whether the content of the wells described in Exhibits 2007 and 2008 are, in fact, transferred to different wells is not determinative. The exhibits do not themselves state that the use of arrows in this way is the "common practice in the art." *See*, *e.g.*, Resp. 19. We recognize that Patent Owner draws that conclusion from Exhibits 2007 and 2008 but, against all the other evidence

in the entire trial record, Patent Owner's conclusion is little more than unpersuasive attorney argument. *Supra* Section II.D.

In sum, Petitioner's Motion to Exclude is dismissed as moot for Exhibits 2003, 2004, and 2006, and denied for Exhibits 2007 and 2008.

IV. MOTION TO AMEND

Patent Owner filed a Contingent Motion to Amend (Paper 21), Petitioner opposed this motion (Paper 27) and Patent Owner filed a Reply (Paper 31). As noted above (Section I.A.), shortly before the Oral Hearing, Patent Owner requested that its Contingent Motion to Amend be withdrawn. Paper 42. The Board granted Patent Owner's unopposed request to withdraw the Contingent Motion to Amend. Paper 43.

V. CONCLUSION

For the reasons above, we determine Petitioner has established, by a preponderance of the evidence, that: (i) claims 1, 3, 5, 6, 10–15, 17, 24–26, 31, 34, 37, and 44 are unpatentable under § 103 over Freskgård (Ground 2), over Freskgård and Pedersen (Ground 3), and over Freskgård and Franch '929 (Ground 4); and (ii) claims 1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45 of the '381 patent are unpatentable under § 103 over Freskgård combined with Franch '427 (Ground 7).

By a preponderance of the evidence on this record, we conclude that Petitioner has not established that the challenged claims of the '381 patent are unpatentable based on Grounds 1, 5, and 6.

Petitioner's Motion to Exclude Evidence is denied as to Exhibits 2007 and 2008, and dismissed as moot on Exhibits 2003, 2004, and 2006.

Patent Owner's Contingent Motion to Amend has been withdrawn.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has proved by a preponderance of the evidence that claims 1, 3, 5, 6, 10–15, 17, 23–26, 31, 34, 37, 44, and 45 of U.S. Patent No. 8,951,381 are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 36) is *dismissed* as moot for Exhibits 2003, 2004, and 2006, and *denied* for Exhibits 2007 and 2008; and

FURTHER ORDERED that, because this is a Final Written Decision, parties seeking judicial review of this Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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