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United States District Court
For the Northern District of California

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA

ILLUMINA, INC., and ILLUMINA
CAMBRIDGE LTD.,

Plaintiffs,

v.

QIAGEN, N.V., QIAGEN GmbH,
QIAGEN GAITHERSBURG, INC.,
QIAGEN SCIENCES, LLC, QIAGEN
INC. (USA), QIAGEN REDWOOD CITY,
INC., and INTELLIGENT BIO-
SYSTEMS, INC.,

Defendants.

No. C 16-02788 WHA

**ORDER GRANTING
MOTION FOR
PRELIMINARY INJUNCTION**

INTRODUCTION

In this patent infringement action involving DNA sequencing technology, the patent owner moves for a preliminary injunction. For the reasons stated below, the motion for a preliminary injunction is **GRANTED**.

STATEMENT

Plaintiff Illumina Cambridge, Inc., owns U.S. Patent No. 7,566,537, which covers “Labelled Nucleotides.” Plaintiff Illumina, Inc., is the exclusive licensee of the ’537 patent. Illumina and Illumina Cambridge (collectively, “Illumina”) sell DNA sequencing equipment that practices the ’537 patent (Van Oene Decl. ¶ 6).

Defendant Qiagen N.V. and several of its subsidiaries, defendants Qiagen GmbH, Qiagen Gaithersburg, Inc., Qiagen Sciences, LLC, Qiagen Inc. (USA), Qiagen Redwood City, Inc., and Intelligent Bio-Systems, Inc. (collectively, “Qiagen”), jointly developed and

1 announced the launch of a competing product, the GeneReader NGS System, with plans to
2 begin distribution later this year. Illumina now seeks to enjoin sales of Qiagen’s GeneReader
3 products.

4 Before discussing the details of the technology at issue herein, some background on the
5 science of DNA is necessary.

6 **1. DNA.**

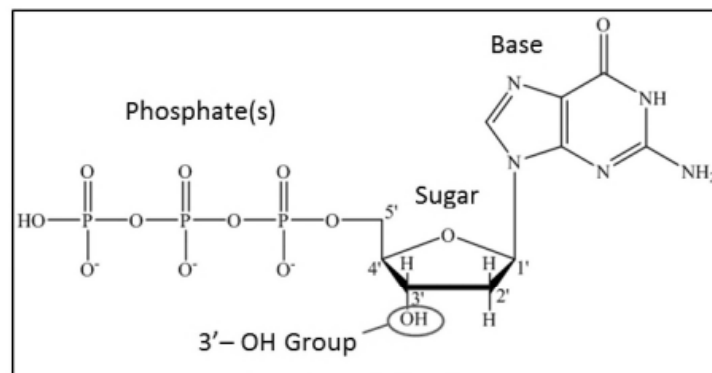
7 DNA, which stands for deoxyribonucleic acid, encodes the genetic material of most
8 organisms. DNA comprises a double helix of strands of linked molecules called nucleotides.
9 Each nucleotide contains a sugar, a phosphate, and one of four different chemical bases, adenine
10 (“A”), cytosine (“C”), guanine (“G”), and thymine (“T”). The bases pair with each other — A
11 with T and C with G — and the two strands of the double helix are held together by the bonds
12 between complementary bases. In other words, each side of a DNA double helix is a perfect
13 complement of the other. The sequence of the bases in a DNA strand reflects genetic
14 information (Metzker Decl. ¶¶ 28–31).

15 As stated, each nucleotide contains a sugar chemical group, which is a ring comprising
16 five carbon atoms. By convention, the carbon atoms are numbered one prime (1') through five
17 prime (5'), and each such atom can be bound to another atom or chemical group, depending on
18 the specific kind of sugar used in that nucleotide. The nucleotides in DNA use the sugar
19 deoxyribose. Deoxyribose has a hydroxyl group (one hydrogen atom and one oxygen atom) at
20 the 3' position (known as a “3'-OH group”). Deoxyribose has only a hydrogen atom at its 2'
21 position. The name deoxyribose indicates the lack of an oxygen atom at the 2' group as
22 compared to ribose, a sugar used in a different kind of genetic material known as RNA, which
23 has a hydroxyl at the 2' position (as well as at the 3' position).

24 The phosphate group of a nucleotide is attached at the 5' position of the sugar. As
25 stated, the strands of DNA comprise a series of nucleotides. The nucleotides in the series are
26 connected via bonds between the 3'-OH group of the sugar on one nucleotide and the phosphate
27 group of the next nucleotide. This sugar-phosphate bond forms the backbone of each strand of
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1 a DNA double helix, and the pairwise bonds between the bases (A-T and C-G) form the
2 cross-bars of the helix.

3 Below is an image depicting a single nucleotide featuring deoxyribose (Metzker Decl.,
4 Fig. 1):



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12 **G Nucleotide**

13 The chemical group labeled “Base” is a G (guanine) group. The vertices of the sugar
14 ring (labeled 1' through 4') and the additional point extending from the 4' position (labeled 5'),
15 are carbon atoms. They are not labeled with a “C” by convention. The circled 3'-OH group is,
16 as stated, the connecting point between each nucleotide and the phosphate group of the next. It
17 is a key aspect of the technology herein, to which this order now turns.

18 **2. SEQUENCING-BY-SYNTHESIS.**

19 Because DNA contains two perfectly complementary strands of nucleotides, the full
20 sequence of DNA can be determined by identifying the sequence of bases in the nucleotides on
21 one of the strands and inferring (from the A-T/C-G pairing) the sequence of the other strand.
22 One technique, used by both Illumina and Qiagen, for identifying sequence of A, T, C, and G
23 that make up one strand is called “sequencing by synthesis.” This process first involves
24 unwinding the double helix of the DNA sought to be analyzed, retaining one strand as a
25 template, and affixing that template to a surface to maintain stability throughout the sequencing
26 process. Once the template is affixed, an enzyme proceeds along the template, adding
27 complementary nucleotides to an adjacent “primer” strand, which is positioned to be read by the
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1 sequencing device. The enzyme proceeds stepwise until it has added a complementary
2 nucleotide for the entire chain.

3 The nucleotides added in the sequencing-by-synthesis process differ from the natural
4 nucleotides in two critical ways. *First*, each nucleotide is modified to include a chemical label,
5 unique to each base (A, T, C, or G) and attached to that base, that can be detected by an external
6 device, such as by emitting a unique fluorescent display. *Second*, each nucleotide is modified to
7 include a “blocking group” or “protecting group” (the terms are used interchangeably) that
8 prevents further nucleotides from binding with the 3'-OH group of the sugar. This forces the
9 enzyme to pause and wait until the label for a nucleotide has been detected before adding the
10 next nucleotide.

11 Once the nucleotide label has been detected, the label can be removed (to avoid
12 interference with further detection), and, critically for our case, the protecting group can be
13 removed in a manner that leaves the 3'-OH group of the sugar exposed, allowing another
14 nucleotide to be added.

15 The '537 patent claims a method for labeling nucleotides in this manner and specifically
16 using an “azido group” as the protecting group. (The patent does not specifically require
17 *sequencing*.) Specifically, Claim 1 of the patent, the only independent claim asserted herein,
18 reads as follows:

19 A method of labeling a nucleic acid molecule, the method
20 comprising incorporating into the nucleic acid molecule a
21 nucleotide or nucleoside molecule, wherein the nucleotide or
22 nucleoside molecule has a base that is linked to a detectable label
23 via a cleavable linker and the nucleotide or nucleoside molecule
24 has a ribose or deoxyribose sugar moiety, wherein the ribose or
25 deoxyribose sugar moiety comprises a protecting group attached
26 via the 2' or 3' oxygen atom, and said protecting group can be
27 modified or removed to expose a 3' OH group and the protecting
28 group comprises an azido group.

29 An azido group is a chemical group including three nitrogen atoms (N₃), *inter alia*. The
30 set of OH protecting groups comprising an azido group encompasses a broad class of more than
31 one thousand chemical structures (Metzker Decl. ¶ 100). Claim 6 of the patent, which depends
32 from Claim 1, is limited to a single protecting group known as azidomethyl.

1 The patent defines the term “nucleoside” as follows (’537 patent, col. 4, l. 59–63):

2 A “nucleoside” is structurally similar to a nucleotide, but are [sic]
3 missing the phosphate moieties. An example of a nucleoside
4 analog would be one in which the label is linked to the base and
5 there is no phosphate group attached to the sugar molecule.

6 In other words, a nucleoside is a chemical group that, like a nucleotide, includes a sugar and a
7 base, but *unlike* a nucleotide, lacks a phosphate group. Nucleosides are discussed in greater
8 detail in connection with Qiagen’s enablement argument below.

9 **3. QIAGEN’S GENEREADER.**

10 Since Intelligent Bio-Systems became a part of the Qiagen family of companies in 2012,
11 Qiagen repeatedly teased the announcement of DNA sequencing technology, then delayed the
12 launch of the product. In April 2016, however, Qiagen began aggressively marketing its
13 GeneReader NGS system. Qiagen itself stated in its marketing materials that GeneReader
14 worked in the “same way as Illumina’s machines, flooding the sample DNA with fluorescently
15 labeled nucleotides and imaging the results” (Walter Decl., Exh. 1 at 2). Indeed, Qiagen’s
16 manual described a process very similar to the patented invention (*id.*, Exh. 13 at 20). Qiagen’s
17 devices used nucleotides including labels linked to their base via a cleavable linker, and they all
18 used protecting groups that comprised azido groups (Burgess Decl., Appx. 1 at 5–13).

19 Although Illumina established a strong brand in the market for DNA sequencing
20 products, Qiagen’s GeneReader began to compete with several of Illumina’s sequencing
21 products, specifically in targeting clinical laboratories, where affordable desktop sequencing
22 devices had just taken off. Qiagen offered its product based on a novel pricing structure,
23 whereby customers paid per use, rather than purchasing the machine and other ancillary
24 products outright (Van Oene Decl. ¶¶ 13–18, 22–26, 45)

25 **4. PROCEDURAL HISTORY.**

26 In 2012, Intelligent Bio-Systems and non-party the Trustees of Columbia University in
27 the City of New York sued Illumina for patent infringement in the District of Delaware.
28 Illumina asserted counterclaims of infringement of the ’537 patent (pertaining to predecessors
of the GeneReader). After Qiagen N.V. acquired Intelligent Bio-Systems, Illumina added
Qiagen N.V. as a new party in that action and asserted counterclaims against it as well. Qiagen

1 N.V. moved to dismiss for lack of personal jurisdiction, and Illumina voluntarily dismissed all
2 claims against it without prejudice. Illumina maintained its claims against Intelligent Bio-
3 Systems and took some discovery relating to the accused products herein in that case.

4 In 2013, Intelligent Bio-Systems challenged the '537 patent on obviousness grounds in
5 an *inter partes* review proceeding before the Patent Trial and Appeals Board. (The Delaware
6 action was stayed pending that review.) The PTAB instituted review of the patent based on
7 several of the prior art references raised in the petition, but declined to institute review as to
8 others, finding them redundant. The PTAB upheld the validity of the claim, and the Federal
9 Circuit affirmed the decision. See *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*,
10 821 F.3d 1359 (Fed. Cir. 2016).

11 Just two weeks after the Federal Circuit's decision upholding the validity of the
12 '537 patent in May 2016, Illumina commenced this action. It filed the instant motion for a
13 preliminary injunction the same day. While the motion remained pending, defendants moved to
14 transfer the action to the District of Delaware, in deference to an earlier-filed action involving
15 the same patent and defendant Intelligent Bio-Systems. Qiagen N.V. also moved to dismiss for
16 lack of personal jurisdiction. The parties stipulated to a schedule by which the motions to
17 transfer and dismiss would be resolved before the preliminary injunction (Dkt. Nos. 34–35).

18 An order denied the motion to transfer, reserving on a final decision after the conclusion
19 of jurisdictional discovery relating to Qiagen N.V.'s contacts with California as well as with the
20 United States as a whole (Dkt. No. 64). Rather than bear the burden of jurisdictional discovery,
21 Qiagen N.V. consented to personal jurisdiction in this district, and its motion to dismiss was
22 denied as moot (Dkt. Nos. 82–83). This order addresses Illumina's motion for a preliminary
23 injunction. It follows full briefing and oral argument.¹

24
25 ¹ Qiagen seeks leave to file a surreply to address new arguments and evidence concerning irreparable
26 harm and invalidity raised for the first time in Illumina's reply. Qiagen's proposed surreply responds to several
27 arguments raised for the first time in Illumina's reply, but the brief also raises several new arguments not raised
28 in the opposition. Additionally, Illumina objects to Qiagen's proposed surreply, stating the parties agreed to a
briefing schedule pursuant to which Qiagen would not seek to file post-reply submissions unless Illumina filed
declarations and Qiagen took depositions of the declarants. The stipulation referenced does not include such a
limitation, it merely provides such depositions as an option (Dkt. No. 35 at ¶ 4(a)). In its objection, Illumina
identifies several new arguments in Qiagen's surreply.

1 **ANALYSIS**

2 “A preliminary injunction is a ‘drastic and extraordinary remedy that is not to be
3 routinely granted.’” *National Steel Car, Ltd. v. Canadian P. Ry., Ltd.*, 357 F.3d 1319, 1324
4 (Fed. Cir. 2004) (quoting *Intel Corp. v. ULSI Sys. Tech., Inc.*, 995 F.2d 1566, 1568 (Fed. Cir.
5 1993)). A party seeking a preliminary injunction must show: “(1) it is likely to succeed on the
6 merits; (2) it is likely to suffer irreparable harm if the injunction is not granted; (3) the balance
7 of hardships weighs in its favor; and (4) an injunction is in the public interest.” *Apple v.*
8 *Samsung* (“*Apple II*”), 695 F.3d 1370, 1373–74 (Fed. Cir. 2012). This order addresses each
9 factor in turn.

10 **1. LIKELIHOOD OF SUCCESS ON THE MERITS.**

11 Illumina accuses Qiagen of infringing independent Claim 1 and dependent Claims 2–6
12 and 8 with its GeneReader product. Its technical expert, Professor Kevin Burgess, provided a
13 detailed declaration setting forth how each element of each of the asserted claims appears in the
14 GeneReader (Burgess Decl. ¶¶ 49–87). Qiagen does not deny that Illumina is likely to succeed
15 on the merits of showing that the accused products read on each of the asserted claims of the
16 ’537 patent. Instead, Qiagen contends that the patent is invalid.

17 At trial, Qiagen will bear the burden of overcoming the statutory presumption of validity
18 with clear and convincing evidence. At this stage, however, we need “not resolve the validity
19 question, but rather must . . . make an assessment of the persuasiveness of [Qiagen’s evidence]”
20 recognizing that further evidence favoring either side may be presented at trial. *Titan Tire*
21 *Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1377 (Fed. Cir. 2008).

22 The Federal Circuit directs us to “first weigh the evidence both for and against validity”
23 as available at the preliminary injunction stage, then to assess whether there is a “substantial
24 question” concerning the validity of the patent, “meaning that the alleged infringer has
25 presented an invalidity defense that the patentee has not shown lacks substantial merit” *Id.*
26 at 1379. Likelihood of success on the merits is a probability of fifty-one percent or more. That
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The parties’ disregard for the procedures of this Court is disappointing. Nevertheless, this order considers the arguments in Qiagen’s surreply and unauthorized supplemental letter and finds them unavailing.

1 leaves a forty-nine percent likelihood that the accused infringer would succeed, which leaves
2 more than enough room for a “substantial question.” Thus, this focus on the presence
3 (or absence) of a “substantial question” of validity is at odds with the primary inquiry at this
4 stage, which considers *likelihood* of success on the merits.

5 The decision in *Titan Tire* recognized that tension and sought to clarify the appropriate
6 standard. It reiterated the foregoing discussion regarding a substantial question of invalidity,
7 but determined as follows:

8 It is important to remember that, however engaged the court may
9 be in the process of determining whether the alleged infringer has
10 shown a “substantial question” of invalidity as we have explained
11 it, that process does not change the court’s ultimate decision
12 point . . . has the plaintiff established a likelihood of success on
13 the merits? Asking whether the challenger has raised a substantial
14 question of invalidity in the manner we have described may be a
15 useful way of initially evaluating the evidence, but the ultimate
16 question regarding the first preliminary injunction factor remains
17 that of the patentee’s likelihood of success on the merits.

18 *Ibid.* Thus, this order considers whether, in light of the evidence presented by both sides at this
19 stage, Illumina has shown it is *likely* to defeat Qiagen’s invalidity arguments, for which Qiagen
20 will ultimately face the clear and convincing evidence standard. Qiagen argues that the ’537
21 patent is invalid inasmuch as it is obvious in light of the combination of three references in the
22 prior art. It also argues that the ’537 fails to enable a person of ordinary skill in the art to
23 practice the full scope of the claimed invention.

24 **A. Obviousness.**

25 Qiagen argues that the ’537 patent is obvious in light of three prior art references. The
26 three articles of prior art are: (1) Roger Tsien, *et al.*, WO 91/06678 (May 16, 1991) (“Tsien”),
27 (2) Jingyue Jue, *et al.*, U.S. Patent No. 6,664,079 (Dec. 16, 2003) (“Ju”), and (3) Theodora W.
28 Greene & Peter G.M. Wuts, *Protective groups in Organic Synthesis* 246–92 (3d ed. 1999)
 (“Greene & Wuts”). To establish that a patent claim is obvious, a challenger must show that all
of the claimed elements were known in the prior art and that a skilled artisan “would have been
motivated to combine the teachings of the prior art references to achieve the claimed invention,
and that the skilled artisan would have had a reasonable expectation of success in doing so.”

1 *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012) (citations
2 omitted).

3 Both Tsien and Ju described modified nucleotides, such as those claimed in the
4 '537 patent, that comprised a base linked to a detectable label that could be removed, a
5 protecting group at the 3' position, and the ability to remove the protecting group to expose a 3'-
6 OH group, though neither Tsien nor Ju identified azido groups as viable removable protecting
7 groups. Additionally, Tsien and Ju utilized a procedure for removing a protecting group that
8 required a high level of efficiency — a limitation not present in the '537 patent.

9 Qiagen's obviousness argument turns on whether a skilled artisan would have found it
10 obvious to combine the labeled nucleotides taught by Tsien and Ju with any references to azido
11 groups in Greene & Wuts.

12 As a preliminary matter, Illumina argues that each of our defendants is estopped from
13 asserting the obviousness arguments raised herein, because defendant Intelligent Bio-Systems
14 already unsuccessfully challenged the '537 patent through the *inter partes* review procedure
15 before the PTAB and on appeal at the Federal Circuit. Section 315(e)(2) of Title 35 of the
16 United States Code provides that the petitioner in an IPR proceeding, "or the real party in
17 interest or privy of the petitioner, may not assert . . . in a civil action . . . that the claim is invalid
18 on any ground that the petitioner raised or reasonably could have raised during that inter partes
19 review."

20 Intelligent Bio-Systems identified Greene & Wuts (combined with Ju or Tsien) in its
21 petition, but the PTAB did not institute IPR proceedings as to those references. It instituted the
22 proceedings as to Ju or Tsien in combination with Zavgorodny, and concluded that
23 consideration of Greene & Wuts would have been redundant.

24 The Federal Circuit recently held that statutory estoppel does not apply to grounds
25 raised in a petition but not instituted. *Shaw Industries Group, Inc. v. Automated Creel Systems,*
26 *Inc.*, 817 F.3d 1293, 1300 (Fed. Cir. 2016). Thus, the arguments that Qiagen raises herein,
27 which were not instituted by the IPR, are not barred by Section 315(e)(2). Illumina also offers
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1 no authority supporting its contention that *all* defendants herein are “privies” of Intelligent
2 Bio-Systems, simply because they are all ultimate subsidiaries of the same parent.

3 For the first time in its reply, Illumina argues that common law issue preclusion, rather
4 than the preclusion rules set forth in Section 315(e)(2), prevent Qiagen from advancing this
5 argument. Illumina cites *B&B Hardware, Inc. v. Hargis Industrial*, 575 U.S. ___, 135 S.Ct.
6 1293, 1305 (2015), for the proposition that common law preclusion applies here, but that
7 decision concerned review of a decision at the Trademark Trial and Appeal Board under the
8 Lanham Act, which does not set forth explicit terms for estoppel. *B&B Hardware* specifically
9 noted, “courts may take it as a given that Congress has legislated with the expectation that the
10 principle [of issue preclusion] will apply except when a statutory purpose to the contrary is
11 evident.” *Ibid.* (citing *Astoria Fed. Sav. and Loan Ass’n v. Solimino*, 501 U.S. 104 (1991))
12 (alteration in original).

13 Unlike the Lanham Act, Section 315(e)(2) set forth the bounds of estoppel based on IPR
14 proceedings. Although this order need not conclusively resolve the issue of estoppel at this
15 stage, Illumina is unlikely to prevail in displacing the statutory design of Section 315(e)(2) in
16 favor of the common law. Nevertheless, this order finds Qiagen’s obviousness argument
17 unpersuasive.

18 *Greene & Wuts* is an extensive treatise covering thousands of protecting groups for
19 various purposes including for hydroxyl groups, such as those at the 3' position of deoxyribose.
20 *Greene & Wuts* does teach the use of azidomethyl (the specific azido claimed in Claim 6 of the
21 '537 patent), as a protecting group, but that reference is in a chapter directed at phenols, which
22 are hydroxyl groups but of a different type than the hydroxyl group that appears in nucleotides
23 or nucleosides (Liaw Decl., Exh. 4, *Greene & Wuts* at 260). *Greene & Wuts* offers an entirely
24 separate chapter on aliphatic alcohols, which include the types of hydroxyl groups that appear
25 in nucleotides and nucleosides. That chapter makes no mention of azido groups. Further,
26 Qiagen’s own expert acknowledges that *Greene & Wuts* teaches removal of the azidomethyl
27 group using a compound that would be inappropriate for use with a nucleotide because “it
28 would alter DNA structures” (Metzker Dep. at 161).

1 Qiagen and its expert contend that, rather than looking to the chapter specifically
2 addressing aliphatic alcohols, a skilled artisan would have looked for “azido” in the index of
3 Greene & Wuts to find an appropriate protecting group. Qiagen’s expert herein, Dr. Michael
4 Metzker, asserted that a skilled artisan would have been so motivated because Tsien taught
5 using azido groups to protect a 3'-OH group (Metzker Decl. ¶ 64). But during the IPR
6 proceedings, Qiagen’s expert stated the azido group referenced in Tsien would not have been
7 removable to expose a 3'-OH group (Branchaud Dep. at 101). At his deposition, Dr. Metzker
8 affirmed that Tsien’s reference to azido groups concerned the use of such groups directly
9 connected to the carbon atom at the 3' position, which, if removed, would not expose a 3'-OH
10 group (Metzker Dep. at 102–03).

11 At this stage, Qiagen has made a weak showing that a person of skill in the art would
12 have been motivated to look to the reference to azidomethyl in the phenol chapter of Greene &
13 Wuts to find an appropriate blocking group for the methods described in Tsien or Ju, which
14 addressed aliphatic alcohols, not phenols.

15 Moreover, Greene & Wuts taught that use of the category of compounds that includes
16 azidomethyl (“ethers”) would have been more efficient for use in phenol than in aliphatic
17 alcohols (such as the 3'-OH in a nucleotide) (Liaw Decl., Exh. 4, Greene & Wuts at 248). Thus,
18 even if Tsien or Ju provided adequate motivation to a skilled artisan to have consulted that
19 chapter of Greene & Wuts, that reference would have indicated a low likelihood of success in
20 using azidomethyl in the process taught by Tsien and Ju, which required high-efficiency
21 removal of the 3'-OH protecting group.²

22 In its surreply, Qiagen notes that Claim 6, which specifically claims the use of an
23 azidomethyl as the azido group of Claim 1, was added during the prosecution of the '537 patent.
24 Thus, information adequate to support that claim must have been disclosed in the application *as*

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26 ² Although it did not institute the IPR proceeding as to Green & Wuts, the PTAB acknowledged this
27 aspect of Greene & Wuts as a background reference that supported its rejection of Intelligent Bio-Systems’
28 arguments at the IPR proceeding, and the Federal Circuit affirmed that this reference in Greene & Wuts
“support[ed] a conclusion that the claimed efficiency that allegedly motivated the combination would not be
achieved and that a person of ordinary skill in this field would not have been motivated to use” azidomethyl.
Intelligent Bio-Systems, 821 F.3d at 1368–69.

1 filed. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). The '537
2 patent pointed to Greene & Wuts as a resource for a suitable protecting group, but it did not
3 specifically call out azidomethyl or phenol alcohols. Thus, Qiagen argues that if a skilled
4 artisan would not have looked to the chapter on phenol alcohols and the section about
5 azidomethyl before the '537 patent, reference to Greene & Wuts generally was an inadequate
6 disclosure of azidomethyl in the patent itself. "One cannot disclose a forest in the original
7 application and then later pick a tree out of the forest and say here is my invention." *Id.* at
8 1326–27 (Fed. Cir. 2000). Rather, there must be "blaze marks" directing a person of skill in the
9 art to that particular "tree." *Id.* at 1327.

10 Although there is no support for the assertion that a skilled artisan would have looked to
11 the "azido" entry in the index of Greene & Wuts before the '537 patent, the '537 patent itself,
12 by focusing on azido groups as protecting groups that could be removed leaving an OH-group
13 exposed, would likely have provided the blaze marks that were otherwise absent from the prior
14 art. Because Qiagen raised this argument for the first time in its surreply, Illumina did not have
15 the opportunity to present argument or evidence in response, but this order finds Qiagen's
16 written description argument unpersuasive. In any case, it would only invalidate Claim 6,
17 which is just one of seven claims asserted herein, so Qiagen could not escape liability by
18 succeeding on its written description argument.

19 At this stage, Illumina appears likely to overcome Qiagen's obviousness challenge (and
20 the related written description challenge) particularly in light of the presumption of invalidity
21 and the clear and convincing evidence standard.

22 **B. Enablement.**

23 Section 112(a) of Title 35 of the United States Code provides:

24 The specification [of a patent] shall contain a written description of
25 the invention, and of the manner and process of making and using
26 it, in such full, clear, concise, and exact terms as to enable any
27 person skilled in the art to which it pertains, or with which it is
28 most nearly connected, to make and use the same

27 After arguing that the combination of every element of the inventions claimed by the
28 '537 patent would have been obvious to a skilled artisan based on the prior art, Qiagen reverses

1 field and argues that it would not have been obvious from the specification and prior art how to
2 practice the inventions, that is, the '537 patent itself did not enable a skilled artisan to practice
3 the inventions. Specifically, Qiagen contends that the '537 patent suffered from three
4 enablement deficiencies: (i) it did not teach how to use nucleosides, rather than nucleotides, (ii)
5 it did not teach how to use the full scope of azido protecting groups, and (iii) it did not teach
6 how to use a nucleotide with an azido group attached at the 2' oxygen atom in a nucleotide
7 containing a ribose (or other sugar comprising an oxygen atom at that position). Each is
8 addressed in turn.

9 **(i) Nucleosides.**

10 Qiagen argues that the '537 patent did not adequately teach how to use a nucleoside
11 molecule. Claim 1 recited a method comprising “incorporating into the nucleic acid molecule a
12 nucleotide or nucleoside molecule” As stated, a nucleoside is similar to a nucleotide,
13 except it lacks a phosphate group — the group that binds a nucleotide molecule to the 3'-OH
14 group on the previous nucleotide. Qiagen contends that the '537 patent failed to disclose how a
15 nucleoside could be incorporated into a nucleic acid, as the patent claimed.

16 Experts on both sides acknowledge that a nucleotide might alternatively be referred to as
17 a “nucleoside triphosphate,” indicating that the nucleotide included a nucleoside plus a
18 phosphate group (Romesberg Dep. at 26; Metzker Dep. at 76). Illumina further notes that
19 numerous patents and applications claim the incorporation of a “nucleotide or nucleoside” into
20 a nucleic acid, *including an application by Qiagen’s expert in this very case* (see Walter Decl.,
21 Exh. 9 at 36, 189, Exh. 11). On the other hand, the specification expressly defined a nucleoside
22 as “structurally similar to a nucleotide, but . . . missing the phosphate moieties” ('537 patent,
23 col. 4, l. 59–60).

24 Illumina argues that the patent should be read to reflect the state of the art, namely, that
25 a skilled artisan might alternatively have referred to a nucleotide as a nucleoside moiety
26 combined with a phosphate group. Thus, Illumina argues, because the '537 patent included the
27 claim limitation “nucleotides or nucleosides,” rather than just “nucleotides,” one could not
28 evade a finding of literal infringement by describing the nucleotides in use as nucleoside

1 triphosphates (or some other nucleosides combined with phosphate groups). Qiagen’s only
2 evidence to the contrary is the lame opinion of its expert that even his own patent application
3 was invalid because it claimed the incorporation of nucleotides or nucleosides into a nucleic
4 acid.³

5 Even if Qiagen could ultimately prevail on this point, it would face an additional hurdle,
6 inasmuch as Claim 4 of the ’537 patent (also asserted herein) claims “[t]he method of Claim 1,
7 wherein the nucleotide is a deoxyribonucleotide triphosphate,” thereby specifying the use of a
8 nucleotide, rather than a nucleoside. At oral argument and in an unauthorized letter brief after
9 the hearing, Qiagen argued that Section 112(d) of Title 32 of the United States Code provides,
10 “[a] claim in dependent form shall be construed to incorporate by reference all the limitations of
11 the claim to which it refers.” Thus, Qiagen contends that Claim 4 should be read to cover the
12 incorporation of deoxyribonucleotide triphosphate *or* any nucleosides into a nucleic acid.

13 Section 112(d) requires us to construe a dependent claim as *narrowing* the claim from
14 which it depends. Qiagen contends it requires us to rigidly construe a dependent claim as
15 narrowing antecedent claim only to a point and no further, but Qiagen cites no authority for its
16 position. On the contrary, a skilled artisan would have been more likely to understand Claim 4
17 as electing to use a nucleotide among the choice between nucleotides or nucleosides, and
18 *further* electing to use deoxyribonucleotide triphosphate. Thus, even if Qiagen can show that
19 Illumina failed to enable use of nucleosides, it likely could not escape liability for infringing
20 Claim 4.

21 This order finds that Illumina is likely to succeed in proving that a skilled artisan would
22 have understood the reference to nucleosides in the patent claims to include the nucleosides
23 that, when ultimately combined with a phosphate group, become nucleotides. Qiagen is
24 unlikely to show clear and convincing evidence to the contrary.

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28 ³ Illumina also notes that a nucleoside could be incorporated via chemical synthesis. The parties disagree as to whether the ’537 patent covers chemical synthesis as opposed to just enzymatic synthesis. It is unnecessary to resolve this claim construction issue at this stage.

1 **(ii) Full Scope of Azido Group.**

2 Qiagen argues that Claim 1 (and dependent Claims 2–5 and 8) of the '537 patent are
3 invalid because they encompass a broad set of modified nucleotides that have a “protecting
4 group compris[ing] an azido group,” while an “azido group” could refer to any of more than one
5 thousand chemical groups. Moreover, because each base (A, C, T, or G) may have variant
6 properties that affect their incorporation into a nucleic acid, different azido groups might work
7 better in combination with different bases, compounding the scope of the claim (*id.* ¶¶ 98–100).

8 Although the mere possibility that a claim includes inoperative combinations is not a
9 sufficient basis to invalidate a patent on its own, “if the number of inoperative combinations
10 becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in
11 order to practice the claimed invention, the claims might indeed be invalid.” *Atlas Powder Co.*
12 *v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576–77 (Fed. Cir. 1984). “General and
13 vague” statements that certain claimed combinations might not work are insufficient to support
14 a finding of lack of enablement. *See Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil*
15 *Co.*, 308 F.3d 1167, 1186 (Fed. Cir. 2002).

16 True, the number of combinations encompassed within the claims is significant, but to
17 date, Qiagen has failed to identify *even one* inoperative combination. Rather, it rests solely on
18 the possibility that a large proportion of the total number of combinations *could* be inoperative.
19 Thus, Qiagen is unlikely to show, by clear and convincing evidence, that Illumina failed to
20 enable the full scope of the azido group.⁴

21 **(iii) 2' Protecting Group.**

22 Qiagen's final enablement argument concerns the fact that the '537 patent covers
23 “protecting group attached via the 2' or 3' oxygen atom,” but the specification offers only a
24 general statement that a protecting group of sufficient size and charge to protect the 3' position
25 would also work at the 2' position. Again, Qiagen has not identified a single embodiment that

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28 ⁴ This particular argument would not affect Claim 6 (asserted herein), which provides the additional
 limitation of a particular azido group, azidomethyl. Claim 6 would not survive Qiagen's other two enablement
 arguments or its obviousness argument, but even if Qiagen succeeded on this argument, it would still need to
 succeed on a second invalidity argument to avoid liability.

1 would not work, nor has it provided any evidence beyond the conclusory statements of its
2 experts that a skilled artisan would have needed to undertake undue experimentation to practice
3 this aspect of the claimed invention. Illumina is also likely to overcome this argument.

4 * * *

5 This is a rare and powerful case for the unusual remedy of a preliminary injunction. The
6 validity of the patent-in-suit has been affirmed by the Federal Circuit (albeit without
7 considering all the add-on arguments asserted here), and Qiagen has ignored Illumina’s
8 infringement case. Although Qiagen’s invalidity arguments are not frivolous, this order finds
9 that Illumina is likely to defeat them, particularly in light of Qiagen’s burden to prove invalidity
10 with clear and convincing evidence. Thus, this order finds Illumina is likely to succeed on the
11 merits and now turns to the equitable considerations for a preliminary injunction.

12 **2. IRREPARABLE HARM.**

13 Illumina argues that an injunction is warranted because Qiagen’s introduction of the
14 GeneReader could interfere with Illumina’s brand reputation, usurp long-term business
15 opportunities, and damage customer goodwill. Specifically, Illumina argues that Qiagen’s
16 GeneReader competes with Illumina’s affordable desktop DNA sequencing products in the
17 market for clinical laboratories (Van Oene Decl. ¶¶ 13–18).

18 The market for DNA sequencing in clinical laboratories is expected to grow
19 substantially in the near future, and Qiagen has a foothold in that market due to its other product
20 lines. Now, as the doors to the market have swung open, Qiagen seeks to usurp Illumina’s
21 position in that market with pirated technology. Moreover, potential customers cannot easily be
22 recovered, inasmuch as laboratories purchase new DNA-sequencing equipment infrequently
23 and irregularly, in part because laboratories must win government approval for use of any new
24 DNA-sequencing equipment (*id.* ¶¶ 26–29, 45).

25 Finally, Qiagen seeks to offer an alternative pricing plan — different from the prevailing
26 trend — whereby customers could rent a GeneReader and pay per use, rather than purchasing
27 the device outright.

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1 At this crucial inflection point in the development of the market for DNA sequencing
2 equipment for clinical laboratories, Illumina would suffer irreparable harm if Qiagen were
3 allowed to capture and define the market with pirated technology alongside its preexisting
4 relationships and disruptive business model. *See Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664
5 F.3d 922, 931 (Fed. Cir. 2012). That harm could be compounded if Qiagen’s products perform
6 poorly — a serious prospect supported by the evidence herein (*see* Arnold Dep. at 112–13;
7 Liaw Exh. JJ at 1).

8 Qiagen responds that Illumina’s delay in seeking this injunction (more than four years
9 after it first learned of Qiagen’s GeneReader) undermines its contention that it would suffer
10 irreparable harm absent an injunction. Not so. Qiagen’s launch of the GeneReader was plagued
11 by a series of false starts, delays, and reformulations. Moreover, the validity of the ’537 patent
12 hung in limbo until the Federal Circuit upheld the PTAB’s decision on Intelligent Bio-Systems’
13 IPR challenge — just weeks before Illumina commenced this action.

14 Illumina’s decision to wait until Qiagen’s launch of the product became imminent
15 ensured its infringement case would not rest on shifting sands. Illumina’s motion is well-timed,
16 seeking to halt Qiagen’s assault on the market at its inception, before it can irreparably change
17 the face of the market.

18 After arguing that Illumina waited too long to seek this motion, Qiagen again reverses
19 field and argues that the motion should be denied because Illumina has not *yet* suffered
20 irreparable harm, pointing to internal Illumina documents suggesting that Qiagen would take a
21 year or two to pose a threat (Liaw Decl., Exhs. GG at *16, JJ at 1). On the contrary, Illumina’s
22 internal documents suggest it *already* views Qiagen’s products as a threat and expects Qiagen to
23 become a more significant threat over the next two years absent an injunction (*id.*, Exh. JJ;
24 Walter Reply Decl., Exh. 6). Moreover, Qiagen’s own assessment of its prospects project it
25 will become a significant player in the coming year (Arnold Tr. at 93–95).

26 The purpose of an injunction is not to remedy irreparable harm that has already occurred
27 (plainly, it could not), but to prevent that harm from occurring in the first place. This is not a
28 case in which Illumina has made mere conclusory statements that it will suffer irreparable harm,

1 but rather one in which Illumina has demonstrated a real risk that Qiagen could capture and
2 redefine the market with its pirated technology. Compensation for lost sales will not adequately
3 remedy the harm Qiagen could do to Illumina’s business absent an injunction.

4 **3. BALANCE OF HARDSHIPS .**

5 In evaluating Illumina’s request for a preliminary injunction, we must weigh the harm
6 that it will suffer absent the injunction against the harm that Qiagen will incur if the injunction
7 is granted. *Hybritech Inc. v. Abbot Labs.*, 849 F.2d 1446, 1457 (Fed. Cir. 1988).

8 Both parties are major corporations with multiple streams of revenue. Ironically, after
9 arguing that Illumina would suffer no irreparable harm absent an injunction, Qiagen contends
10 there would be “no way to know the opportunities” Qiagen itself lost during the injunction, and
11 that it would be unable to recoup its investment in the development and marketing of the
12 GeneReader (Defs.’ Opp. at 25). But that is the price of its election “to build a business on a
13 product found to infringe” *Windsurfing Int’l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1003 n.12
14 (Fed. Cir. 1986). The balance of hardships weighs in favor of an injunction.

15 **4. PUBLIC INTEREST.**

16 “[A]bsent any other relevant concerns . . . the public is best served by enforcing patents
17 that are likely valid and infringed.” *Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1348
18 (Fed. Cir. 2006). Qiagen argues that because its product is currently marketed for analysis of
19 cancer-related genes, an injunction could negatively impact cancer research, but Illumina is
20 poised to meet any demand for Qiagen’s product in the wake of an injunction, so that argument
21 is unavailing. Moreover, as clinical laboratories adopt Qiagen’s product, they may grow to rely
22 on the potentially-infringing technology, only to face their own liability following the likely
23 result in this action. Thus, the public interest weighs in favor of an injunction.

24 **CONCLUSION**

25 For the reasons stated above, Illumina’s motion for a preliminary injunction is
26 **GRANTED** as follows:

27 Defendants and their officers, agents, affiliates, employees, and
28 attorneys, and all those persons acting or attempting to act in
concert or participation with them, are enjoined from making,
using, offering to sell, or selling within the United States, or

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importing into the United States, or marketing, promoting, or distributing the Qiagen GeneReader NGS System, as depicted in Plaintiffs' moving papers, or any related product that embodies the claims of U.S. Patent No. 7,566,537 ("the '537 Patent"), such as the GeneRead Sequencing Q Kit (1) or the GeneRead Sequencing Q Kit (4).


Within **TWENTY ONE CALENDAR DAYS**, defendants must promptly notify all United States-based users of the Qiagen GeneReader NGS System, and/or any related product that embodies the claims of the '537 Patent, such as the GeneRead Sequencing Q Kit (1) or the GeneRead Sequencing Q Kit (4), about this order such that these users are duly noticed and bound by this order under Federal Rule of Civil Procedure 65(d)(2).

Qiagen asks that Illumina be required to submit a bond as security for the harm it will allegedly suffer by not being able to market the GeneReader during the pendency of this case pursuant to Rule 65(c). Within **FOURTEEN CALENDAR DAYS**, Illumina must post a bond of twenty million dollars as security for the injunction.

In light of the deluge of unauthorized supplemental materials filed by both sides in relation to this motion, this order hereby establishes a précis system for this case, as follows. Except for discovery disputes, no further motions may be filed in this action without prior written approval. A party seeking approval to file a motion must file a précis that summarizes the essence of the motion and explains its urgency. Any party opposing approval to file based on the précis may file an opposition by noon on the second business day following the day on which the précis was filed. Both the précis and the opposition must not exceed three pages, double-spaced, and may not contain footnotes or attachments. After considering the précis and the opposition (if any), the Court will either grant or deny leave to file the motion. If leave is granted, a briefing schedule and hearing date will be set.

IT IS SO ORDERED.

Dated: September 9, 2016.



WILLIAM ALSUP
UNITED STATES DISTRICT JUDGE