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

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

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

1. DNA.

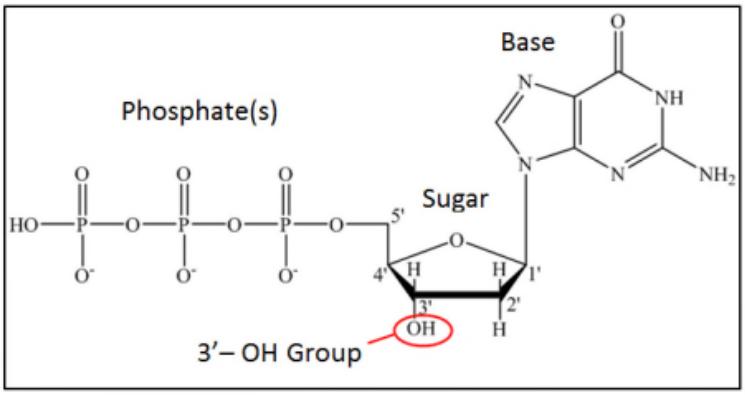
DNA, which stands for deoxyribonucleic acid, encodes the genetic material of most organisms. DNA comprises a double helix of strands of linked molecules called nucleotides. Each nucleotide contains a sugar, a phosphate, and one of four different chemical bases, adenine ("A"), cytosine ("C"), guanine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

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

The phosphate group of a nucleotide is attached at the 5' position of the sugar. As stated, the strands of DNA comprise a series of nucleotides. The nucleotides in the series are connected via bonds between the 3'-OH group of the sugar on one nucleotide and the phosphate group of the next nucleotide. This sugar-phosphate bond forms the backbone of each strand of

a DNA double helix, and the pairwise bonds between the bases (A-T and C-G) form the cross-bars of the helix.

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



G Nucleotide

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

2. SEQUENCING-BY-SYNTHESIS.

Because DNA contains two perfectly complementary strands of nucleotides, the full sequence of DNA can be determined by identifying the sequence of bases in the nucleotides on one of the strands and inferring (from the A-T/C-G pairing) the sequence of the other strand. One technique, used by both Illumina and Qiagen, for identifying sequence of A, T, C, and G that make up one strand is called "sequencing by synthesis." This process first involves unwinding the double helix of the DNA sought to be analyzed, retaining one strand as a template, and affixing that template to a surface to maintain stability throughout the sequencing process. Once the template is affixed, an enzyme proceeds along the template, adding complementary nucleotides to an adjacent "primer" strand, which is positioned to be read by the

sequencing device. The enzyme proceeds stepwise until it has added a complementary nucleotide for the entire chain.

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

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

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

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

An azido group is a chemical group including three nitrogen atoms (N_3), *inter alia*. The set of OH protecting groups comprising an azido group encompasses a broad class of more than one thousand chemical structures (Metzker Decl. ¶ 100). Claim 6 of the patent, which depends from Claim 1, is limited to a single protecting group known as azidomethyl.

The patent defines the term "nucleoside" as follows ('537 patent, col. 4, l. 59–63):

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

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

3. QIAGEN'S GENEREADER.

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

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

4. PROCEDURAL HISTORY.

In 2012, Intelligent Bio-Systems and non-party the Trustees of Columbia University in the City of New York sued Illumina for patent infringement in the District of Delaware. 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

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

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

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

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

[1] Qiagen seeks leave to file a surreply to address new arguments and evidence concerning irreparable harm and invalidity raised for the first time in Illumina's reply. Qiagen's proposed surreply responds to several arguments raised for the first time in Illumina's reply, but the brief also raises several new arguments not raised 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.

ANALYSIS

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

1. LIKELIHOOD OF SUCCESS ON THE MERITS.

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

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

The Federal Circuit directs us to "first weigh the evidence both for and against validity" as available at the preliminary injunction stage, then to assess whether there is a "substantial question" concerning the validity of the patent, "meaning that the alleged infringer has presented an invalidity defense that the patentee has not shown lacks substantial merit . . . ." *Id.* 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.

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

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

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

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

A. Obviousness.

Qiagen argues that the '537 patent is obvious in light of three prior art references. The three articles of prior art are: (1) Roger Tsien, *et al.*, WO 91/06678 (May 16, 1991) ("Tsien"), (2) Jingyue Jue, *et al.*, U.S. Patent No. 6,664,079 (Dec. 16, 2003) ("Ju"), and (3) Theodora W. Greene & Peter G.M. Wuts, Protective groups in Organic Syntheis 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."

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

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

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

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

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

The Federal Circuit recently held that statutory estoppel does not apply to grounds raised in a petition but not instituted. *Shaw Industries Group, Inc. v. Automated Creel Systems, Inc.*, 817 F.3d 1293, 1300 (Fed. Cir. 2016). Thus, the arguments that Qiagen raises herein, which were not instituted by the IPR, are not barred by Section 315(e)(2). Illumina also offers

no authority supporting its contention that *all* defendants herein are "privies" of Intelligent Bio-Systems, simply because they are all ultimate subsidiaries of the same parent.

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

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

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

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

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

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

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

[2] Although it did not institute the IPR proceeding as to Green & Wuts, the PTAB acknowledged this aspect of Greene & Wuts as a background reference that supported its rejection of Intelligent Bio-Systems' 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.

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

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

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

B. Enablement.

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

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

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

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

(i) Nucleosides.

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

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

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

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

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

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

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

[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.

(ii) Full Scope of Azido Group.

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

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

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

(iii) 2' Protecting Group.

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

[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.

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

* * *

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

2. IRREPARABLE HARM.

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

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

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

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

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

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

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

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

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

3. BALANCE OF HARDSHIPS .

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

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

4. PUBLIC INTEREST.

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

CONCLUSION

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

> Defendants and their officers, agents, affiliates, employees, and 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

> 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