UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 24-11697-RGS

BIOMODAL LIMITED and CHILDREN'S MEDICAL CENTER CORPORATION

v.

NEW ENGLAND BIOLABS, INC.

MEMORANDUM AND ORDER ON PLAINTIFFS' MOTION FOR A PRELIMINARY INJUCTION and DEFENDANT'S MOTION TO DISMISS

November 25, 2024

STEARNS, D.J.

Plaintiffs biomodal Limited (biomodal) and Children's Medical Center Corporation (CMCC) filed this action against defendant New England Biolabs, Inc. (NEB), accusing it of infringing U.S. Patent Nos. 10,337,053 B2 ('053 patent); 10,443,091 B2 ('091 patent); 10,533,213 B2 ('213 patent); 10,731,204 B2 ('204 patent); 10,774,373 B2 ('373 patent); 10,767,216 B2 ('216 patent); 11,072,818 B2 ('818 patent); and 11,208,683 B2 ('683 patent). Before the court are two motions: (1) plaintiffs' motion for a preliminary injunction prohibiting NEB from marketing allegedly infringing products; and (2) defendant's motion to dismiss the claims of the '204, '213, '818, '373 and '683 patents as embodying unpatentable subject matter under 35 U.S.C.

§ 101.[1] For the following reasons, the court will allow in part and deny in part the motion to dismiss and deny the motion for a preliminary injunction.

MOTION TO DISMISS

I. The Patents

Epigenetics is the study of changes in gene expression that are not encoded in DNA – in other words, how environmental and behavioral factors impact the function of genes without changing the underlying sequence of the DNA. One of the most common epigenetic modifications is the methylation of DNA. This is often performed by using 5-azacytidine, one of the several analogs for the nucleoside cytidine, to create 5-methylcytosine (5mC). 5mC may further be oxidized into 5-hydroxymethylcytosine (5hmC).

5mC and 5hmC occur naturally and are often associated with diseases like cancer, making detection and quantification of these modifications medically significant. The asserted patents, which share substantially the same specification and claim priority to the same provisional application, address this issue. They are directed to "novel methods for regulating and detecting the cytosine methylation status of DNA." '213 patent, abstract.

[1] NEB does not move to dismiss the claims of the '053, '091, or '216 patents.

NEB challenges the following claims from the asserted patents:[2]

'818 patent

1. A method comprising contacting with, or delivering to a nucleic acid sequence, an enzyme or fragment thereof that oxidizes at least one methylated DNA base, in an amount effective to convert 5-methylcytosine to 5-hydroxymethylcytosine.

'204 patent

1. A method of converting a methylated cytosine residue in an isolated nucleotide sequence to a modified base, the method comprising:

contacting said isolated nucleotide sequence with an enzyme or a catalytically active fragment thereof that converts said methylated cytosine residue in said isolated nucleotide sequence to said modified base, wherein said modified base comprises a hydroxymethylated cytosine residue,

wherein said enzyme or said catalytically active fragment thereof comprises TET1, TET2, TET3, CXXC4, a catalytically active fragment of any of these, or any combination thereof.

. . .

[2] The court declines, at this early stage in the litigation, to find the recited claims representative of their respective patents. Plaintiffs identify additional limitations which could possibly render some of the remaining claims eligible, and in any event, these claims are not currently asserted in this action and are thus not before the court. Should that change – if, for example, plaintiffs move for leave to amend the Complaint to add back the dismissed counts under the aegis of a different claim – it remains open to NEB to oppose on the grounds that the newly asserted claims are directed to ineligible subject matter under § 101.

3. The method of claim 1, further comprising detecting a methylation status of said isolated nucleotide sequence based on a presence or an absence of said modified base.

'213 patent

1. A method for detecting a 5-methylcytosine residue in a nucleic acid, the method comprising:

(a) oxidizing the 5-methylcytosine residue in the nucleic acid to generate a modified nucleic acid, wherein the oxidizing comprises contacting the nucleic acid with TET1, TET2, TET3, CXXC4, a catalytically active fragment of any of these, or any combination thereof; and

(b) detecting the modified nucleic acid, wherein detection of the modified nucleic acid is indicative of a presence of the 5-methylcytosine residue in the nucleic acid.

'373 patent

1. An isolated nucleic acid from an extracellular fluid sample, wherein a hydroxymethylated cytosine of said isolated nucleic acid is glucosylated.

'683 patent

1. A composition comprising a mixture of a methylcytosine dioxygenase, a DNA glucosyltransferase, and nucleic acid comprising glucosylated 5-hydroxymethylcytosine.

II. Legal Standard

"To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'" *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009), quoting *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007). Two basic principles guide the

court's analysis. "First, the tenet that a court must accept as true all of the allegations contained in a complaint is inapplicable to legal conclusions." *Iqbal*, 556 U.S. at 678. "Second, only a complaint that states a plausible claim for relief survives a motion to dismiss." *Id.* at 679. A claim is facially plausible if its factual content "allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Id.* at 678.

III. Discussion

While "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," may be eligible for patent protection, 35 U.S.C. § 101, "'laws of nature, natural phenomena, and abstract ideas' are not patentable," *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 70 (2012), quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). Courts apply a two-step framework to evaluate subject matter eligibility:

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat else is there in the claims before us?" To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application. We have described step two of this analysis as a search for an "'inventive concept'" – i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Alice Corp. Pty. v. CLS Bank Int'l, 573 U.S. 208, 217-218 (2014), quoting *Mayo*, 566 U.S. at 72-73, 78, 79.

a. Count III

Count III asserts infringement of claim 1 of the '818 patent, which recites a method of exposing "a nucleic acid sequence" to "an enzyme . . . that oxidizes at least one methylated DNA base" in "an amount effective" to convert 5mC to 5hmC. NEB argues that this claim fails the first step of *Alice* because it recites no more than a law of nature, namely, the natural reaction that occurs when 5mC is exposed to certain enzymes. Def.'s Mem. in Supp. of Mot. to Dismiss (Def.'s Mem.) [Dkt # 55] at 8.

The court agrees. At its core, the claim does nothing more than replicate the natural process of "an enzyme . . . that oxidizes at least one methylated DNA base," '818 patent, cl. 1, oxidizing 5mC into 5hmC. It thus claims ineligible subject matter. *See PureCircle USA Inc. v. SweeGen, Inc.*, 2024 WL 20567, at *5 (Fed. Cir. Jan. 2, 2024) ("To the extent that claim 14 claims a 'method for making Rebaudioside X comprising a step of converting Rebaudioside D to Rebaudioside X using a UDP-glucosyltransferase,' it claims a natural phenomenon. The enzyme in claim 14, UGT76G1, is naturally found in stevia plants and naturally converts Reb D to Reb X.").

Attempting to avoid this inexorable outcome, plaintiffs trumpet in their opposition the "amount effective" language of the claim, arguing that "[a]dministering the recited 'effective' amount is not a naturally occurring phenomenon or a natural law" but instead involves a proactive treatment step. Pls.' Opp'n to Mot. to Dismiss (Pls.' Opp'n) [Dkt # 69] at 18. But the Supreme Court has expressly rejected the proposition that simply applying a natural law in a therapeutic context renders it eligible for patenting. *See Mayo*, 566 U.S. at 78; *see also SAP Am., Inc. v. InvestPic, LLC*, 898 F.3d 1161, 1169 (Fed. Cir. 2018) ("[L]imitation of the claims to a particular field of information . . . does not move the claims out of the realm of abstract ideas."). To satisfy § 101, the claim must "do significantly more than simply describe these natural relations." *Mayo*, 566 U.S. at 78.

It follows that, if the claim does nothing more than recite a natural process, it fails to satisfy the "inventive concept" requirement of step two. The court accordingly will dismiss Count III of the Complaint.

b. Count II

Count II asserts infringement of claims 1 and 3 of the '204 patent. Claim 1 of the '204 patent recites a "method of converting" 5mC "in an isolated nucleotide sequence" to 5hmC by exposing the sequence to one or more of the TETI, TET2, TET3, or CXXC4 enzymes. Claim 3 of the '204

patent incorporates the method of claim 1 but adds the limitation of "detecting" the "methylation status" of the "isolated nucleotide sequence" by measuring the presence or absence of 5hmC.

Although claims 1 and 3 parallel the claim invalidated above, plaintiffs assert that a different result is warranted with these claims. This is so, they maintain, because the claimed method "creates a modified, non-naturally occurring nucleotide sequence" which is "unnaturally rich in 5hmC and unnaturally deficient in 5mC." Pls.' Opp'n at 7. The problem is this: The claims are not directed to the allegedly new, modified nucleotide sequence identified by plaintiffs.[3] Rather, they target the same replication of a natural process that the court earlier found ineligible.[4] The court will accordingly dismiss Count II for the same reasons it dismissed Count III.

[3] The court does not mean to imply that claims directed to the modified nucleotide sequence *would* be eligible for patenting under § 101. All the court holds is that claims 1 and 3 are *not* directed to any such modified nucleotide sequence.

[4] Although the parties do not meaningfully distinguish between claims 1 and 3 in their filings, *see* Def's Mem. at 8-11; Pls.' Opp'n at 7-13, the court further notes that the addition of the detection step recited in claim 3 adds nothing to the underlying law of nature. It simply tells the user to detect the results of the natural process "through whatever process the doctor or the laboratory wishes to use." *Mayo*, 566 U.S. at 79.

c. Count I

Count I asserts infringement of claim 1 of the '213 patent, which recites a "method for detecting" 5mC "in a nucleic acid" by: (a) exposing the nucleic acid to at least one of the enzymes TET1, TET2, TET3, or CXXC4 "to generate" 5hmC; and (b) using the presence or absence of 5hmC in the nucleic acid to detect 5mC. Although framed in terms of detection rather than conversion, this claim, like the ones above, is directed to the natural oxidization of 5mC into 5hmC once it is exposed to certain enzymes. The court accordingly will dismiss Count I for the same reasons discussed earlier.

d. Count VI

Count VI asserts infringement of claim 1 of the '373 patent. The claim recites "[a]n isolated nucleic acid from an extracellular fluid sample" in which at least one 5hmC "is glucosylated." NEB contends that this claim is directed to ineligible subject matter because glucosylated 5hmC exists in nature. Plaintiffs do not dispute that it exists in bacteriophages, but they contend that this is irrelevant because the claim is limited to nucleic acid *extracted from extracellular fluid* and, according to plaintiffs, 5hmC in nucleic acid taken from extracellular fluid *cannot* naturally be glucosylated prior to extraction.

The court reserves any ruling on this aspect of the parties' dispute. The issue can be resolved only with the benefit of discovery into the factual question of whether the 5hmC in nucleic acid from extracellular fluid can in fact be naturally glucosylated prior to extraction.[5]

e. Count IV

Count IV asserts infringement of claim 1 of the '683 patent, which recites a "composition comprising a mixture of methylcytosine dioxygenase [*i.e.*, an oxidizing enzyme], a DNA glucosyltransferase, and nucleic acid comprising glucosylated" 5hmC. Although the parties appear to agree that the various components of the mixture exist in nature, there is a dispute of fact as to whether the combination itself exists in nature. It is also not clear to the court whether, if the combination does *not* exist in nature, there is something in the art of mixing these components together that is sufficient to confer patent eligibility, even though they appear to perform the same function in the composition as they do in isolation. Thus, consistent with the court's decision as to claim 1 of the '373 patent, the court reserves any ruling on the patentability of claim 1 of the '683 patent pending discovery.

[5] And, if it cannot, whether there is something inventive in applying the natural glucosylation process in the extracellular fluid context. NEB persuasively asserted during the November 21, 2024 hearing that the answer is no, but the court will reserve a ruling pending factual discovery.

MOTION FOR A PRELIMINARY INJUNCTION

Plaintiffs move for a preliminary injunction based on alleged infringement of claim 3 of the '204 patent, claim 1 of the '683 patent, claim 1 of the '053 patent, and claim 1 of the '091 patent. "To obtain a preliminary injunction, a party must establish likelihood of success on the merits, likelihood it will suffer irreparable harm absent preliminary relief, the balance of equities tips in its favor, and an injunction is in the public interest." *Natera, Inc. v. NeoGenomics Lab'ys, Inc.*, 106 F.4th 1369, 1375 (Fed. Cir. 2024). The burden is "on the movant to show that it is likely to succeed on the merits." *BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391, 1398 (Fed. Cir. 2022).

Plaintiffs falter at the first step.[6] "To show likelihood of success on the merits, a patentee must show '(1) it will likely prove infringement and (2) its

[6] The court also entertains doubt about whether plaintiffs have shown irreparable harm, given the availability of monetary damages and the cautionary recent Supreme Court decision reminding district courts of the extraordinary and rare grant of this equitable remedy. *See Starbucks Corp. v. McKinney*, 144 S. Ct. 1570, 1576 (2024). And as defendant forcibly argued at the hearing, plaintiffs have not met their burden of showing that an injunction would serve rather than harm the public interest. Given that the parties to the litigation are the sole suppliers of the accused products, plaintiffs' inability to convincingly demonstrate their capacity to scale up production to meet the vacuum that an injunction would create in the current market demand is a near-fatal concession on this prong of the injunctive standard.

infringement claim will likely withstand challenges to the validity and enforceability of the patents.'" *Natera*, 106 F.4th at 1375, quoting *Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1363 (Fed. Cir. 2001). Plaintiffs have not shown that the second element is met here.[7]

"An accused infringer 'need not make out a case of actual invalidity' to avoid a preliminary injunction but need only show a substantial question of invalidity." *Natera*, 106 F.4th at 1376, quoting *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1359 (Fed. Cir. 2001). A substantial question of invalidity is one that "the patentee cannot prove 'lacks substantial merit.'" *Entegris, Inc. v. Pall Corp.*, 490 F.3d 1340, 1351 (Fed. Cir. 2007), quoting *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1364 (Fed. Cir. 1997). The very fact that the court has already found claim 3 of the '204 patent invalid and has reserved ruling on claim 1 of the '683 patent shows the existence of a substantial question of invalidity with respect to these patents. As for the asserted claims of the '053 and '091 patents, plaintiffs have not shown that NEB's invalidity defenses, regardless of their

[7] The court expresses no opinion as to whether plaintiffs have shown that they will likely prove infringement.

ultimate merits (the court expresses no opinion on this issue), lack substantial validity.[8] The motion accordingly must be denied.

ORDER

For the forgoing reasons, the motion to dismiss is ALLOWED IN PART and DENIED IN PART and the motion for a preliminary injunction is DENIED. Counts I, II, and III are dismissed, and Counts IV and VI shall, for time being, proceed to factual discovery.

SO ORDERED.

/s/ Richard G. Stearns
UNITED STATES DISTRICT JUDGE

[8] Indeed, plaintiffs do not even address NEB's argument that claim 1 of the '091 patent fails to enable the claimed invention or provide sufficient written description of it. *Compare* Def.'s Opp'n to Pls.' Mot. for a Prelim. Inj. [Dkt #37] at 23-24, *with* Pls.' Reply to Def. Def.'s Opp'n to Pls.' Mot. for a Prelim. Inj. [Dkt # 52] at 9-10.