UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

Oxford Immunotec Ltd.,

Plaintiff,

v.

Qiagen, Inc. et al.

Defendant.

Action No. 15-cv-13124-NMG

REPORT AND RECOMMENDATION ON DEFENDANTS' JOINT MOTION TO DISMISS (Dkt. No. 36)

CABELL, U.S.M.J.

This is an action for infringement of six patents related to a method for diagnosing tuberculosis. The plaintiff, Oxford Immunotec, Ltd., develops tests to diagnose and monitor patients with auto-immune diseases. Defendants Qiagen, N.V. and Qiagen, Inc. are alleged to have infringed the plaintiff's patents by developing their own tuberculosis test. The remaining defendants, Quest Diagnostics, Inc. and Laboratory Corporation of America Holdings, are alleged to have infringed the plaintiff's patents by using and selling the allegedly infringing product the Qiagen defendants developed. (Dkt. No. 1).

Currently before the court is the defendants' joint motion to dismiss. The motion is premised on the argument that the defendants' affirmative defense of patent invalidity is certain

to succeed because the plaintiff's patents are drawn to a law of nature. As discussed below, I recommend that the motion be allowed in part and denied in part.

I. SCIENTIFIC BACKGROUND AND PATENTS[1]

An antigen is a molecule produced by a pathogen (*e.g.*, bacteria), that produces an immune response in the host organism. In the human immune system, T-cells are white blood cells that can recognize pathogens by recognizing the antigens that the pathogens produce. A T-cell that has seen a particular pathogen is "antigen-experienced." When it encounters that pathogen again, it will activate to fight it. One part of that activation is the production of cytokines, which are small proteins that have a specific effect on the interactions and communications between cells. The cytokines produced by T-cells signal other types of cells in the immune system, which respond to the site of the infection to assist in attacking the responsible pathogen.

Mycobacterium tuberculosis ("*M. tuberculosis*") is the bacterium that causes tuberculosis (TB). *M. tuberculosis* produces a unique protein (*i.e.*, antigen) called ESAT-6. ESAT-6, like all proteins, is composed of a chain of peptides, which are naturally occurring chains of two or more amino acids.

The patents-in-suit teach a method for *in vitro* diagnosis of TB. *In vitro* diagnosis occurs in a test tube outside the human body. In contrast, the prevailing method of diagnosing TB is an *in vivo* skin test where TB antigens are injected into the patient's arm.

The plaintiff's test uses specified concentrations of eight peptides that are components of ESAT-6. The peptides are synthetic (*i.e.*, made in a lab), but their amino acid makeup is the

[1] The facts in this section are taken from the plaintiff's complaint and the patents-in-suit, which are attached as exhibits to the complaint. (Dkt. No. 1). As it is required to do at the motion to dismiss stage, the Court accepts the facts alleged by the plaintiff as true. Because there has not yet been a claims construction hearing in this case, the Court construes all patent claims in the manner most favorable to the plaintiff as the non-moving party.

same as the peptides that occur naturally in ESAT-6. The eight-peptide panel is "contact[ed]" with "a population of T cells from the host" and it is "determin[ed] *in vitro* whether T cells in the T cell population show a recognition response to the panel by detecting an IFN- γ [interferon gamma] secretion from the T cells." In other words, the eight peptides are mixed with the test subject's blood in a test tube and the doctor observes whether the T cells produce cytokines, a response that occurs only if the T cell has seen *M. tuberculosis* before.

Before the plaintiff developed its *in vitro* blood test, there was no such *in vitro* diagnostic test for TB in common use. Instead, there were two standard methods for diagnosing TB. The Mantoux tuberculosis skin test (TST), involves injecting a small amount of TB protein derivative into a patient's forearm and then observing the injection site 48 to 72 hours after the injection. A positive TST test indicates that a patient has been infected with TB bacteria. A sputum culture – collecting and culturing phlegm from the upper respiratory tract – is used to determine whether an infected patient actually has TB as distinguished from a latent infection. The patented *in vitro* test is superior to prior *in vivo* skin tests because it is faster, more convenient, less dependent on the administering physician's subjective judgment, and has a lower rate of false positives.

The complaint asserts that the defendants have infringed six of the plaintiff's patents. United States Patent No. 7,632,646, entitled "Tuberculosis Diagnostic Test" ("the'646 patent"), was issued on December 15, 2009. United States Patent No. 7,901,898, entitled "Tuberculosis Diagnostic Test" ("the '898 patent"), was issued on March 8, 2011. United States Patent No. 8,216,795, entitled "Tuberculosis Diagnostic Test" ("the '795 patent"), was issued on July 10, 2012. United States Patent No. 8,507,211, entitled "Tuberculosis Diagnostic Test" ("the '211 patent"), was issued on August 13, 2013. United States Patent No. 8,617,821, entitled "Assay Method for Peptide Specific T-Cells" ("the '821 patent"), was on December 31, 2013. United

States Patent No. 9,005,902, entitled "Tuberculosis Diagnostic Test" ("the '902 patent"), was issued on April 14, 2015.

II. DEFENDANTS' MOTION AND PLAINTIFF'S OPPOSITION

The defendants jointly move to dismiss the complaint on the grounds that an affirmative defense they have asserted, the defense of patent invalidity, will inevitably succeed because the plaintiff's patents are drawn to non-patentable subject matter, specifically products or laws of nature. Their motion divides the claims in the patents-in-suit into "kit claims" and "method claims," and separately addresses each category.

As to the kit claims, the defendants argue that the peptides used in the plaintiff's tuberculosis test kit are naturally occurring (as part of ESAT-6) and therefore are products of nature. The defendants rely on *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013), where the Supreme Court held that isolated DNA sequences were not patentable, to argue that identifying, isolating and mixing together certain peptides did not change the peptide panel into something other than a product of nature.

As to the method claims, the defendants argue that the plaintiff's *in vitro* method of using the peptide panel kits to test for infection does not involve an "inventive concept" because: 1) the steps specified in the method are inherent to practicing the natural law; and 2) the testing methods are routine and conventional methods that were well known before the patents were issued. (Dkt. No. 37).

The plaintiff argues that its peptide panel is not a product of nature because the peptides are synthetic and function differently from naturally occurring ESAT-6. Specifically: 1) the peptides directly activate T-cells without the need for antigen presenting cells; 2) the plaintiff selected particular peptides from ESAT-6 rather than the whole protein; and 3) synthetic peptides

elicit a T-cell response that is different from the one elicited by naturally occurring ESAT-6. The plaintiff also suggests that its *in vitro* testing method is not a product of nature because *in vitro* testing is, by definition, performed in the artificial conditions of a laboratory. The plaintiff argues that even if the peptide panel is held to be a product of nature, its method of using the panel to test for TB *in vitro* is a substantial improvement over the prevailing skin test because it is faster and yields fewer false positive results. (Dkt. No. 43). The plaintiff has submitted a declaration of a medical expert explaining why its product is an improvement over prior technology, suggesting that the plaintiff believes that this matter cannot be resolved on the pleadings. (Dkt. No. 44).

III. DISCUSSION

A. Legal Standard

A defendant may move to dismiss a complaint under Federal Rule of Civil Procedure 12(b)(6) where the complaint fails to "state a claim to relief that is plausible on its face." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007). Though the usual basis for a 12(b)(6) motion is the plaintiff's failure to plead sufficient facts in its complaint, a motion to dismiss "may sometimes be premised on the inevitable success of an affirmative defense." *Nisselson v. Lernout*, 469 F.3d 143, 150 (1st Cir. 2006).

Here, the defendants argue that the plaintiff's patents are invalid under 35 U.S.C. § 101 because they are drawn to laws of nature, and that their affirmative defense of patent invalidity will inevitably succeed. For the defendants to obtain dismissal on this basis, the Court must find that "the only plausible reading of the patent" is one that demonstrates that the patent claims cover subject matter that is not eligible for patenting. *Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d

1335, 1339 (Fed. Cir. 2013); *OIP Techs., Inc. v. Amazon.com, Inc.*, 788 F.3d 1359, 1364 (Fed. Cir. 2015).

B. Analysis

Federal law sets out the requirements of patent eligibility. *See* 35 U.S.C. § 101.[2] However, "[e]xcluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). The underlying concern is that patents covering such elemental concepts would reach too far and claim too much, on balance obstructing rather than catalyzing innovation. But this concern must also be balanced against the risk that an overly aggressive application of these exceptions could swallow patent law entirely. Because "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," the Court should not be too quick to conclude that a patent is drawn to one of these exceptions. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012).

To balance these competing concerns, the Supreme Court in *Mayo* created a two-step inquiry for determining when an invention has patentable subject matter. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (citing *Mayo Collaborative Servs.*, 132 S. Ct. 1289). First, the court determines if the asserted claims are directed at patent ineligible subject matter, such as something drawn to a law of nature. *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355. If the subject matter is ineligible, the Court then asks, "[w]hat else is there in the claims before us?" *Mayo Collaborative Servs.*, 132 S. Ct. at 1297. "To answer that question, [the Court] consider[s] the elements of each claim both individually and as an ordered combination to determine

[2] 35 U.S.C. § 101 provides that: "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

whether the additional elements transform the nature of the claim into a patent-eligible application." *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355 (internal quotations omitted). Courts commonly refer to step two of the analysis as a search for an "inventive concept," which is "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 natural law itself." *Mayo Collaborative Servs.*, 132 S. Ct. at 1294. As the Federal Circuit has recognized in the context of the abstract idea exception, "[d]istinguishing between claims that recite a patent-eligible invention and claims that add too little to a patent-ineligible . . . concept can be difficult, as the line separating the two is not always clear." *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1255 (Fed. Cir. 2014).

1. The Patents are Drawn to a Law of Nature

In this case the Court must first determine whether the claims at issue are directed to a law of nature. The Court concludes that they are. Specifically, the claims are drawn to ESAT-6, a naturally occurring protein, and the human immune system's naturally occurring response to ESAT-6.

The main consideration when determining if something is drawn to a law of nature is whether the claimed product is transformed into something different than how it exists in nature. *See Diamond v. Chakrabarty* 447 U.S. 303, 310 (1980); *Gottschalk v. Benson*, 409 U.S. 63, 70 (1972); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 137 (1948). *Chakrabarty* demonstrates when subject matter is patent eligible. *See Chakrabarty,* 447 U.S. at 310. The inventors in *Chakrabarty* created a new bacterium with the ability to break down crude oil, a trait that no other bacterium possesses in nature. *Id.* This characteristic was one of "human ingenuity 'having a distinctive name, character [and] use.'" *Id.* at 309-10 (citation omitted). *Funk*

Brothers provides further insight into determining patent-eligibility. Farmers would inoculate their crops with bacteria in order to have the nitrogen affix to the soil, but different inoculants had to be used on different crops because certain bacteria inhibited the nitrogen fixing abilities of other bacteria. *Funk Brothers*, *333* U.S. at 128-30. They discovered that six species of bacteria existed that could be mixed together but would not inhibit one another. *Id*. at 130. When mixed together, the bacteria acted differently than each would alone, but nothing was done to the individual strands of bacteria such that they were any different than they were in their naturally occurring state. *Id.* The Supreme Court found that the bacteria served the same "ends nature originally provided" and concluded that the composition of the strands was not patentable. *Id.* at 131.

In *Myriad*[3] the Supreme Court addressed the isolation of DNA as patentable subject matter. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117 (2013). The relevant claim at issue in *Myriad* was related to the isolation of the BRCA1 and BRCA2 genes from a larger strand of DNA. *Id.* The Supreme Court found the claim to be naturally occurring because a portion of DNA is still naturally occurring even though chemical bonds have been broken in order to isolate that portion. *Id.* at 2111 ("It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2. The location and order of the nucleotides existed in nature before Myriad found them."). The Supreme Court additionally found the claims to not be patent eligible because they did not "rely in any way on the chemical changes that result from the isolation of a particular section of DNA." *Id.* at 2118.

[3] The plaintiffs argue at length that *Myriad* and other cases holding that isolated DNA sequences are products of nature are inapplicable because DNA serves a purely "informational" function while the proteins at issue here are "functional." The Court does not find this distinction to be material. As discussed, the decision in *Myriad* turned on the fact that isolated DNA segments exist in nature, albeit as part of a larger DNA strand. As this Court reads *Myriad*, it was that fact – and not the informational function of DNA – that compelled the Supreme Court's ultimate conclusion. The Court therefore finds the reasoning of *Myriad* and other cases like it applicable and instructive here.

As the motion to dismiss is broken down by kit and method claims, the Court's analysis accordingly addresses each argument separately.

a. Kit Claims

The "kit claims" describe kits for diagnosing TB infection that are comprised of a specific panel of peptides. The kit claims are claim 7 of the `646 patent, claim 7 of the `898 patent, and claim 17 of the `795 patent. The defendants argue in reliance on *Myriad* that the peptides in question are drawn to a law of nature because they have been isolated the same way the BRCA1 and BRCA2 genes were isolated. (Dkt. No. 37). The plaintiff argues contrarily that *Myriad* supports its position because the inventors there were using the genes for the same informational purpose that they carried in the larger strand of DNA and were not relying on any chemical change that occurred. (Dkt. No. 43). In contrast, the plaintiff contends that its peptide panels do act differently when isolated from the larger ESAT-6 strand. (*Id.*)

While the Court appreciates that isolated peptides perform differently than peptides contained in an intact ESAT-6 strand, the Court does not find this fact significant to its analysis. The inquiry at step one of the *Mayo* analysis is whether the peptides are drawn to patent ineligible subject matter. Applied here, the question is whether the peptides exist in nature or whether, instead, they have been changed from their natural state. It is undisputed that the peptides have not been changed beyond the act of isolation. The Court thus finds that the isolated peptides are products of nature.

This conclusion is further bolstered by the language of the patents-at-issue, which makes it plain that the isolated peptides exist as they do in nature. For example, the `646 patent states, "the inventors have found ***8 peptides from the ESAT-6 protein of M. tuberculosis*** which are recognized by the T cells of a high proportion of patients with tuberculosis." (emphasis added).

This language is also found in the '898 Patent, the '795 Patent, the '211 Patent, and the '902 Patent. Though the peptides used in the panel are synthetically created, this language confirms that their makeup is wholly based upon the structure of ESAT-6, which is naturally occurring.

b. Method Claims

The method claims are claim 1 of the `211 panel, claim 1 of the `902 patent, and claims 1 and 6 of the `821 panel. They describe a method for using the peptide panel kits to conduct an *in vitro* test for TB infection. The method claims teach that T-cells from the patient can be contacted with the peptide panel kit and then tested for IFN- γ, which will be naturally produced by the body in patients who have previously been infected with TB.

When the peptide panel kit is used to test for TB infection, the isolated peptides do act differently than ESAT-6 in certain respects. Specifically, the isolated peptides are able to obtain a response from CD4 T-cells and CD8 T-cells, while ESAT-6 only obtains a response from CD4 T-cells. The isolated peptides are also capable of binding to the T-cells without an antigen-presenting cell or MHC cells, both of which are required when the reaction occurs in the body.

Despite these differences in how the immune system reaction occurs, however, the end result of both reactions is the same, the body's production of IFN- γ. The Court thus concludes that the plaintiff's method claims are drawn to a law of nature: T-cells that have previously been exposed to *M. tuberculosis* will excrete IFN- γ.

2. The Claimed Inventions Involve an "Inventive Concept"

Moving on to step two of the *Mayo* analysis, the issue is whether the plaintiff's invention, which "focuses upon the use of a natural law," is nonetheless patent-eligible because it "also contains other elements or a combination of elements . . . sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Mayo*

Collaborative Servs., 132 S. Ct. at 1294. In order to be considered inventive, a concept must go beyond "well-understood, routine, conventional activity, previously engaged in by those in the field." *Id*. at 1299. An invention that "improve[es] an existing technological practice," or "solve[s] some technological problem in conventional industry practice" fits this definition. *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2358; *Versata Dev. Group., Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1334 (Fed. Cir. 2015) (both differentiating their facts from *Diehr*, 450 U.S. 175, where the patented invention improved on existing technology); *cf. Mayo Collaborative Services*, 132 S. Ct. at 1298 (patent that identified a law of nature -- what metabolite range indicated an overdose of a drug versus an under-dose – and directed physicians to test patients' blood metabolite levels lacked an inventive concept because blood metabolite level tests were routine even before the patent-holder discovered the precise metabolite levels that should be tested for).

Here, the plaintiff has discovered a law of nature – namely which specific peptides in ESAT-6 are most likely to induce a recognition response by the T-cells of patients who have TB without creating false positive responses by the T-cells of those who have merely been vaccinated. The question therefore is whether plaintiff's process of combining its panel of selected peptides with a patient's blood in a test tube and then measuring cytokine production is an inventive process that adds enough to the natural law to bring the patent claims into the realm of patentable material. The plaintiff's complaint alleges that Oxford's patented inventions provide a "faster and more reliable method of diagnosing TB infection," than the conventional means available at the time of the invention," the TST and sputum culture. (Dkt. No. 1). The patents-in-suit state that the only TB tests in "general use" before the plaintiff's invention were the TST and sputum culture. (*Id*.). Accepting these allegations as true, the Court finds that the patented invention improves on existing methods for diagnosing TB by making diagnosis more

convenient, less dependent on a physician's subjective interpretation of results, and more accurate. There is thus a plausible reading of the patents by which one could find that the plaintiff's *in vitro* tuberculosis test involves an inventive concept.

The Court understands that the defendants dispute both the plaintiff's claims construction and the extent to which *in vitro* tests similar to the plaintiff's were in use before the patents-in-suit were issued. But these arguments are premature at the motion to dismiss stage, where the court must "accept[] as true all well-pleaded facts, analyz[e] those facts in the light most hospitable to the plaintiff's theory, and draw[] all reasonable inferences for the plaintiff." *Hutcheson v. Blackstone Med., Inc*., 647 F.3d 377, 383-84 (1st Cir. 2011).

At this early juncture, the Court concludes that the *in vitro* aspect of the plaintiff's tuberculosis test is an "inventive concept" because it improves on prior methods of detecting tuberculosis infection. It follows that the method claims, which describe the *in vitro* test, are potentially drawn to patentable subject matter. In contrast, the kit claims only describe the peptide panel itself and do not involve the "inventive concept" of an *in vitro* test, and thus are not drawn to patentable subject matter.

IV. CONCLUSION

Based upon the foregoing, the Court recommends that the defendants' motion to dismiss be ALLOWED insofar as it seeks dismissal of the plaintiff's claims for infringement of the kit claims, and DENIED in all other respects. The parties are hereby advised that under the provisions of Federal Rule of Civil Procedure 72(b), any party who objects to this recommendation must file specific written objections thereto with the Clerk of this Court within 14 days of the party's receipt of this Report and Recommendation. The written objections must specifically identify the portion of the proposed findings, recommendations, or report to which

objection is made and the basis for such objections. The parties are further advised that the United States Court of Appeals for this Circuit has repeatedly indicated that failure to comply with Rule 72(b) will preclude further appellate review of the District Court's order based on this Report and Recommendation. *See Keating v. Secretary of Health and Human Servs.*, 848 F.2d 271 (1st Cir. 1988); *United States v. Emiliano Valencia-Copete*, 792 F.2d 4 (1st Cir. 1986); *Park Motor Mart, Inc. v. Ford Motor Co.*, 616 F.2d 603 (1st Cir. 1980); *United States v. Vega*, 678 F.2d 376, 378-379 (1st Cir. 1982); *Scott v. Schweiker*, 702 F.2d 13, 14 (1st Cir. 1983); *see also Thomas v. Arn*, 474 U.S. 140 (1985).

/s/ Donald L. Cabell
DONALD L. CABELL, U.S.M.J.

DATED: August 31, 2016