NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY, *Plaintiff,* v. QIAGEN N.V. and QIAGEN, INC., *Defendants.*	Civil Action No.: 15-cv-7187 (PGS)(LHG) **MEMORANDUM AND ORDER**

SHERIDAN, District Judge.

Facts and Procedural History:

Rutgers, the State University of New Jersey ("Rutgers") owns patents for the detection in humans exposed to the mycobacterium that causes tuberculosis (Mycobacterium tuberculosis) ("TB"). (Complaint ("Compl.") at 1.) The methods and compositions can detect the difference between infection by TB and vaccination by the Bacille Calmette Guerin (BCG) strain of Mycobacterium bovis. BCG is the strain of bovine tuberculosis most commonly used to vaccinate humans. *Id.* Rutgers brings this action against Qiagen N.V. and Qiagen, Inc. (collectively "Qiagen") for infringement, contributory infringement, and/or inducement of infringement of those patents. (Compl. ¶ 1.) Qiagen N.V. is a Dutch company doing business in the United States through its subsidiary, Qiagen, Inc. (Id.) Qiagen N.V. was voluntarily dismissed without prejudice on January 4, 2016 (ECF No. 16).

Rutgers inventor Maria Gennaro, M.D. discovered these methods and compositions for the detection of the TB infection that discriminate between humans that have been exposed to

TB and those who have been vaccinated with BCG. (Id ¶ 8.) The inventions use in vitro methods, meaning a blood sample is drawn and then exposed to certain polypeptide antigens that are specific to TB and are not found in BCG. (Id.) These antigens are recognized by T-cells of a person previously exposed to or infected with TB, causing the T-cells to secrete cytokines, including interferon-γ ("IFN-γ"); and detection of IFN-γ with an agent such as an antibody allows for the diagnosis of TB exposure and/or infection. (Id.) On August 25, 2009, the U.S. Patent and Trademark Office issued U.S. Patent No. 7,579,141 ("the 141 patent"). (Id. ¶ 10.) On September 20, 2011, Patent No. 8,021,832 ("the '832 patent") was issued. (Id. ¶ 11.) On March 10, 2015, U.S. Patent No. 8,974,800 ("the '800 patent") was issued. (Id. ¶ 12.) Rutgers is the assignee and owner for each. (Id.)

Defendant's diagnostic kits QFT and QFT-Plus also involve exposing blood to peptide antigens to stimulate expression of IFN-γ by T-cells. The detection of express IFN-γ is accomplished by using enzyme-linked immunosorbent assay ("ELISA") technology. (Id. ¶ 9.)

According to Plaintiff, the specific peptides and MHC (Major Histocompatibility Complex) molecules involved in antigen presentation and T-cell activation are different for each person, even when responding to the same pathogen. (Ehrt Decl. ¶¶ 16-17.) As a result, diagnostic tests need to account for this diversity. (Id. ¶ 25.) The inventions in this case respond to this problem by eliminating the need for antigen presenting cells in the assay. Plaintiff asserts that "the claimed inventions use polypeptides, or antigenic segments thereof, that do not occur in nature, to simulate MTBN4 and ESAT-6 (both are pathogenic proteins produced by M. tuberculosis) and elicit detectable levels of T cell stimulation and IFN-γ release as an indicator of tuberculosis infection." (Plaintiff's Brief, at 7.)

The only practical way to diagnose TB before these inventions was the tuberculin skin test ("TST"), according to Rutgers. TST is an in vivo skin test whereby tuberculosis antigens are injected into the patient's forearm, and then the site is inspected days later to look for irritation, which would point to an immune response and possible TB infection. (Ehrt Decl. ¶¶ 26-27.) The downsides to this approach are that multiple patient visits are required, it is slow working, and it results in a subjective analysis. (Id. ¶ 27.) It is also prone to false positives in individuals previously inoculated with the BCG TB vaccine. (Id.) According to Plaintiff, the patented in vitro tests has essentially replaced the TST test. (Id. ¶¶ 28-33.) The in vitro blood tests are done in a single visit, allowing for objective measurement of cytokines (like IFN-γ) to signify T cell activation and infection. (Id. ¶ 29.)

Legal Standard:

On a motion to dismiss for failure to state a claim pursuant to Fed. R. Civ. P. 12(b)(6), the Court is required to accept as true all allegations in the Complaint and all reasonable inferences that can be drawn therefrom, and to view them in the light most favorable to the non-moving party. *See Oshiver v. Levin, Fishbein, Sedran & Berman,* 38 F.3d 1380, 1384 (3d Cir. 1994). "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, 127 S. Ct. 1955, 167 L. Ed. 2d 929 (2007)). While a court will accept well-pleaded allegations as true for the purposes of the motion, it will not accept bald assertions, unsupported conclusions, unwarranted inferences, or sweeping legal conclusions cast in the form of factual allegations. *Iqbal*, 556 U.S. at 678-79; *see also Morse v. Lower Merion School District*, 132 F.3d 902, 906 (3d Cir. 1997). The question is whether the claimant can prove any set of facts consistent with his or her

allegations that will entitle him or her to relief, not whether that person will ultimately prevail. *Semerenko v. Cendant Corp.*, 223 F.3d 165, 173 (3d Cir.), *cert. denied, Forbes v. Semerenko*, 531 U.S. 1149, 121 S. Ct. 1091 (2001).

In opposition to the motion to dismiss, Rutgers provides the Declaration of Sabine Ehrt, a Professor in the Department of Microbiology and Immunology at the Weill Medical College of Cornell University, with exhibits ("Ehrt Decl"). On a 12(b)(6) motion, a court generally only considers the complaint, matters referenced in the Complaint, and attachments. A court may consider "matters integral to or upon which plaintiff's claim is based." *In re Bayside Prison Lit.*, 190 F. Supp. 2d 755, 760 (D.N.J. 2002). "The reason that a court must convert a motion to dismiss to a summary judgment motion if it considers extraneous evidence submitted by the defense is to afford the plaintiff an opportunity to respond." *Pension Ben. Guar. Corp. v. White Consol. Indus., Inc.* 998 F.2d 1192, 1196 (3d Cir. 1993). If a complaint relies on a document, "the plaintiff obviously is on notice of the convents of the document, and the need for a chance to refute evidence is greatly diminished." *Pension Ben.*, 998 F. 2d at 1196-97. Plaintiff submitted these documents, they are integral to the Complaint, and they are also helpful in responding to facts outlined in Defendant's motion to dismiss regarding the science at issue. Therefore, the Court will consider this declaration.

Analysis:

Patent-eligibility under 35 U.S.C. § 101 has a two-part test. First, the court looks to whether the claims are directed to patent ineligible subject matter, like laws of nature, natural phenomena or abstract ideas. *Alice Corp Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014). Second, the court must determine whether the application is patent-eligible, by considering "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." *Alice*, 134 St. Ct. at 2355. "Put another way, there must be a further 'inventive concept' to take the claim into the realm of patent-eligibility." *In re BRCA1-and BRCA2-Based Hereditary Cancer Test Patent Litigation ("BRCA1")*, 774 F.3d 755, 763 (Fed. Cir. 2014).

I. First, Defendant argues that the method claims of the '141 and '832 patents are drawn to patent ineligible naturally-occurring proteins, phenomena and immune molecules. "Phenomena of nature, though just discovered, mental processes, and abstract ideas are not patentable, as they are the basic tools of scientific and technological work." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012). Products of nature like isolated DNA are not patent-eligible subject matter, as well as isolated parts of naturally occurring products of nature. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013).

The method claims are all meant to detect molecules that are created by an individual's immune system by responding to the presence of naturally occurring proteins from the TB bacteria, according to Defendant. Defendant further argues that all of the molecules in these claims identified for detection are naturally occurring: lymphocytes, cytokines produced by lymphocytes, and antibodies. Defendant cites to *Myriad*, which held that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated." 133 S. Ct. at 2111.

Plaintiff contends that the inventions are not drawn to "naturally occurring" peptides or immune responses. The '800 patent claim term "isolated polypeptide" is defined to include a polypeptide which has "no naturally-occurring counterpart or has been separated or purified from components which naturally accompany it." '800 patent (D.I. 1-4) at col. 3, ll. 38-41. According

to Plaintiff, neither the peptide or antigenic segments or its surroundings are naturally occurring. Plaintiff claims that there is no chance that any of the polypeptides or antigenic segments thereof in the compositions or methods are found in a human because a protein consists of hundreds of amino acids. Since the cleavage of each protein is random, the probability of creating an identical peptide to one in the in vitro assay is approximately one in every 10,000, and this probability is further diminished because cleavage is not random in nature. (Ehrt Decl. ¶ 22.)

In addition, Plaintiff claims that its in vitro assay uses artificial conditions that do not occur in nature. The in vitro assay is done outside the body, in a lab using a test-tube, and performed by using biological molecules and cells. (Ehrt Decl. ¶ 20.) In vivo assays, on the other hand, evaluate "biological processes as they are observed to occur in their natural environment, i.e. within living organisms." *Id.* According to Plaintiff, the in vitro assays usually create artificial activity not observed in vivo, such as "elevated reagent concentrations, or receptor binding sites, which are not found in vivo." *Id.* ¶ 21. Also, the compositions and tests include polypeptides that activate T cells, which does not occur in nature in vivo. *Id.* ¶¶ 22-24.

Plaintiff also claims that the polypeptides or antigenic segments in the compositions and methods are functionally distinct from naturally occurring MTBNs (polypeptide antigens). Plaintiff states that the patents are different from naturally occurring T cell activation, because the patents here do not require APCs (antigen presenting cells) and can synthetically directly bind and activate the T cells. Second, naturally occurring MTBNs, which require APC in vivo, and the polypeptides of the assays at issue, which do not require APC in vivo, cause different T cell responses. Third, the composition here allows detection of antigen-specific T cells in vitro in blood, and do not create antigen-specific T cells like in nature. (Ehrt Decl. ¶¶ 19-25.) Therefore, according to Plaintiff, these patents are the "product of human ingenuity," causing processes that

are "markedly different...from any found in nature" and "having the potential for significant utility." *Diamond v. Chakrabarty*, 447 U.S. 303, 309-310 (1980).

Plaintiff claims that it is illogical that its inventions would be ineligible simply because they involve elements found in nature, such as MTBN4, ESAT-6, T cells and IFN-γ, because such a proposition would cause almost all inventions to be un-patentable. S*ee Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 132 S. Ct. 1289, 1293 (2012) ("all inventions at some level embody, use, reflect, rest upon, or apply laws of nature and natural phenomena").

Plaintiff distinguishes the case law relied upon by Defendant that analogizes the proteins at issue with DNA. In *Myriad*, the Supreme Court held that DNA sequences are informational molecules, and the information character of DNA is not altered by isolating it, according to Plaintiff. *See Myriad*, 133 S. Ct. at 2120 ("We merely hold that genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material.") This holding furthered the purpose of § 101, according to Plaintiff, which is not to impede "the flow of information." *Id.* at 2116. Plaintiff objects to Defendant's argument that DNA and proteins should be treated similarly because they both have "sequences." Isolating a sequence of DNA will not change its informational character, nor its ability to bind complementary sequences, according to Plaintiff. On the other hand, proteins and polypeptides are "molecular machines" whose activity is "highly dependent on its surrounding environment." (Ehrt Decl. ¶¶ 36-37.) Also, unlike DNA, isolated proteins and peptides usually have different properties in vitro. Combinations of proteins and peptides changes the "sensitivity and reactivity of the molecules," according to Plaintiff. (Plaintiff's Brief, at 17.) Additionally, the Federal Circuit has noted that DNA sequences and amino acid sequences of the proteins encoded by DNA are not the same. *See Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir.

1997) ("Although a close relationship exists between a DNA construct and the protein it encodes, the two are not equal.") Plaintiff emphasizes the "functional" character of the peptides as compared to the informational character of DNA.

In its reply brief, Qiagen argues that it is undisputed that in 1995, four years before the filing of the patents, a paper was published stating 1.) that BCG did not share some proteins found in TB; 2.) where the proteins were located in the TB genome; and 3.) that the proteins could be used for diagnostic tests. At most, the Rutgers inventor may have been the first to discover MTBN-4 (which may not be true), but that is naturally occurring and patent-ineligible, according to Defendant. Defendant's Reply, at 4. Also, in oral argument, Qiagen emphasized that the ELISA test is a common product in the field, and there is nothing inventive about it use.

Qiagen also objects to Rutgers argument that the holdings in *Myriad*, *Mayo*, *Ariosa* and *BRCA1* are limited to DNA-based claims. In *Mayo*, the metabolite naturally produced by the body in response to administration of a drug was not DNA and still not patent eligible, according to Qiagen. Also, even though DNA and proteins or peptides have different functions, they both consist of repeating blocks of molecules that result in sequences. Defendant asserts that the nucleotides in DNA (A, G, T and C) correspond to the amino acids in proteins/peptides.

The Court concludes that Defendant has not satisfied its burden for a motion to dismiss. While the case is close, it is at least plausible that the materials used in the inventions are not all naturally-occurring, since Plaintiff states that it highly unlikely for them to combine in this form. It also became evident during oral argument that there are factual questions about whether the added antigenic peptides are "synthetic." Qiagen claims that these are merely multiple naturally-occurring snapshots of portions of proteins, while Rutgers argues that it highly difficult and

inventive to produce the combinations of peptides here. Either way, the case for patentability is stronger in the next part of the analysis.

II. The next step is to see whether the combination of steps individually or as a whole "transform the nature of the claim into a patent-eligible application." *Alice*, 134 S Ct. at 2355 (internal quotations omitted). Applying known methods to detect or analyze the naturally occurring phenomena does not satisfy this step. *BRCA1*, 744 F.3d at 762.

Defendant asserts that the method claims at issue here are similar to those in *Ariosa*, which were meant to detect cell-free fetal DNA, a naturally-occurring type of fetal DNA that had previously been unknown. *Ariosa*, 788 F.3d at 1373. The Federal Circuit held that the methods to detect this DNA were known prior to the invention, stating that "where claims of a method patent are directed to an application that starts and ends with a naturally occurring phenomenon, the patent fails to disclose patent eligible subject matter if the methods themselves are conventional, routine and well understood applications in the art." *Id.* at 1378. Plaintiff also distinguishes *Ariosa*, where the invention was only the application of a "combination of known laboratory techniques" to a new discovery to determine fetal characteristics. *Id.* at 1373. Plaintiff states: "Here the patent claims entail the use of 'molecular machines,' proteins and peptides (many of them synthetic/non naturally occurring), to perform non naturally occurring biological reactions in *in vitro* blood samples obtained from humans..." (Plaintiff's Brief, at 18.)

Rutgers contends that the claimed inventions were not "routine," "conventional," "well-known," or "widely used." Previously, in vivo skin tests were the norm, and these were replaced by the in vitro blood tests. Also, a concept is considered "inventive" under § 101 where it "improve[s] an existing technological process," "solve[s] some technological problem in conventional industry practice," or achieves a "new and useful end." *Alice*, 134 S. Ct. at 2358;

Versata Dev. Group., Inc. v. SAP Am., Inc., 793 F.3d 1306, 1334 (Fed. Cir. 2015); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). The Rutgers inventions satisfy this test by greatly improving upon the prior practice, according to Plaintiff.

The Supreme Court has said that the main "concern that drives this exclusionary principle is one of pre-emption." *Alice*, 134 S. Ct. at 2354. In *Mayo Collaborative Servs. v. Prometheus Labs.*, the patent was "set forth in highly general language covering all processes that make use of the correlations." 132 S. Ct. at 1302. In this case, Plaintiff claims that the inventions are limited to the specific application of a diagnosis of human TB infections, only involve certain antigens (MTBN polypeptides or antigenic segments), and cause a T cell activation response. There are other polypeptides and cytokines involved in diagnosing TB, and there appear to be alternatives to this procedure, according to Plaintiff. (Ehrt Decl. ¶ 38; Ex. 11 at p. 1475.)

Finally, Plaintiff claims that the Patent Office issued the '800 patent under a tougher standard than § 101. The Office issued the patent after using the *Mayo* and *Myriad* courts. (Ehrt Decl. Ex. 2.) For the '800 patent, five of out the six factors in favor of patent eligibility were met, and all six of the factors that weigh against patent eligibility were not.

Qiagen contends that the combination of various naturally-occurring proteins in a composition does not make it patent-eligible if the proteins are not changed. *Myriad,* 113 S. St. Ct. at 2117. In *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), the Supreme Court looked at a composition that mixed a naturally occurring strain of bacteria to facilitate consumption of nitrogen from the air by certain plants to help them fix it in the soil, and declared it patent ineligible. 333 U.S. at 128-129. Defendant claims that each protein in the '800 patent is naturally occurring, and when combined the proteins keep their individual identities.

Qiagen argues that the inventions are not patent eligible simply because they are in vitro. First, according to Qiagen at oral argument, the patents do not even rely upon the in vitro analysis. Moreover, according to Defendant, these in vitro tests were known prior to the inventions, even if they were not widely used: "the most that Plaintiff can and does argue is that the test platforms claimed in the patent had not been used for detecting the presence of immune cells that were responsive to TB as opposed to BCG." (Defendant's Reply Brief, at 8.)

The Court finds that Rutgers has presented sufficient facts to survive the motion to dismiss. It is plausible that the invention does not simply isolate or identify a material found in nature. While in vitro tests had previously existed, it seems that the inventor applied that test in a new and unique way in order to significantly improve the process for detecting TB as opposed to BCG. Also, the special characteristics of proteins as compared to those of DNA may support patent-eligibility. Patentability is bolstered by the fact that the Patent Office applied the more stringent standards in *Mayo* and *Myriad* to the '800 patent and found that the invention was patent-eligible. At this stage of the case, Rutgers merely has to establish that its claim is plausible, and the Court determines that it has done so.

ORDER

This matter having come before the Court on a Motion to Dismiss by Defendant Qiagen, Inc. [ECF No. 10]; and the Court having considered the submissions of the parties, having heard oral argument, for the reasons set forth on the record, and for good cause shown,

It is, on this 29 day of February, 2016, hereby

ORDERED that the Motion to Dismiss is **DENIED**.

PETER G. SHERIDAN, U.S.D.J.