IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS, L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO,	)	
	)	C.A. No. 15-572-GMS
Plaintiffs,	)	
v.	)	
MERCK & CO., INC. and MERCK SHARP & DOHME CORP.,	)	
Defendants.	)	

DEFENDANTS MERCK & CO., INC. AND MERCK SHARP & DOHME CORP.'S BRIEF SUPPORTING THEIR MOTION TO DISMISS

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INTRODUCTION

Defendants move to dismiss this case because the patent in suit, U.S. Patent No. 9,073,994 (the "'994 patent"), claims ineligible subject matter. *See* 35 U.S.C. § 101. The patent claims are drawn to a natural phenomenon and do not reflect any inventive contribution.

The natural phenomenon is the body's own mechanism for regulating the immune system. T cells, which are part of the immune system, attack and kill cells that the immune system sees as foreign, including cancer cells. To do this, T cells first become activated against the foreign cells. To prevent activated T cells from mistakenly attacking normal cells, the body has mechanisms for shutting down these activated T cells. One mechanism is the PD-1 pathway, and it is triggered when normal cells produce proteins called PD-1 "ligands." The PD-1 ligands on normal cells interact with a protein on the T-cells called the PD-1 receptor. When that occurs, these activated T cells are shut down, and the immune system's mistaken response against normal cells is suppressed.

Before the purported invention of the '994 patent, scientists knew that certain types of cancer cells avail themselves of this natural biological pathway to evade destruction by the immune system. That is, the cancer cells act like normal cells by producing PD-1 ligands that shut down T cells and prevent T cells from attacking them. Scientists also understood that disabling the PD-1 pathway restored the ability of the T cells to do what they normally do, namely, attack the "foreign" cancer cells without being shut down.

The claims in the '994 patent add nothing to this natural phenomenon. They recite treating melanoma by giving the patient an antibody that binds to the PD-1 receptor and is "effective" to treat the metastatic melanoma. But the patent claims define no novel characteristics or properties of the antibody beyond the circular statement that it should be effective to treat melanoma. It merely claims the result of a natural phenomenon: when PD-1

ligands do not engage the PD-1 receptor the body's T cells attack cancer cells as they normally do, but when the ligands do engage, the T cells are shut down. The claims of the '994 patent thus claim ineligible subject matter under 35 U.S.C. § 101, as applied by *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), because they are directed to a natural phenomenon and recite no inventive contribution beyond the natural phenomenon itself.

The Complaint talks at considerable length about nivolumab, a specific anti-PD-1 antibody marketed by one of the plaintiffs, Bristol-Myers Squibb Co., which has recently received FDA approval for treating certain melanoma patients. But, notably, nivolumab is not identified or described anywhere in the '994 patent. Nor could it have been. Nivolumab was invented separately, by different scientists working for a different company than the company that employed the '994 patent's inventors. Moreover, the nivolumab antibody is claimed separately in other patents assigned to Bristol-Myers Squibb Co. and Ono Pharmaceutical Co., which claim priority to patent applications filed almost three years after the first patent application to which the '994 patent claims priority.[1]

This is not a case where a patent claims a novel use of a class of compounds based on their properties or characteristics. Rather, it is one in which the patent claims define the compounds to be used exclusively by reference to whether they cause the desired natural phemonenon to occur – in other words, they claim nothing more than the natural phenomenon itself.

In these circumstances, the Complaint does not state a plausible infringement claim and should be dismissed with prejudice pursuant to Federal Rule of Civil Procedure 12(b)(6).

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[1] *See, e.g.*, Ex. 1, U.S. Patent No. 8,779,105. All exhibits cited in this brief are identified in and attached to the Declaration of John G. Day filed contemporaneously herewith.

NATURE AND STAGE OF THE PROCEEDINGS

Plaintiffs Bristol-Myers Squibb Co., E. R. Squibb & Sons, L.L.C., Ono Pharmaceutical Co., Ltd., and Tasuku Honjo filed this action on July 7, 2015. (D.I. 1.) The Complaint asserts a single claim for relief, alleging infringement of U.S. Patent No. 9,073,994 ("the '994 patent") by Defendants Merck & Co., Inc. and Merck Sharp & Dohme Corp. (collectively, "Merck"). (*Id.* at ¶¶ 26–31.) Specifically, Plaintiffs allege that Merck induces or contributes to infringement of the '994 patent by making and selling pembrolizumab, which Merck sells in the United States under the name Keytruda® for treatment of some patients with melanoma, a type of cancer. (*Id.* at ¶¶ 19–25, 29.) The '994 patent is titled "Immunopotentiative Composition," and its claims are directed to methods of treating a metastatic melanoma. (D.I. 1-1.)

By stipulation and Court order, the deadline for Merck to respond to the Complaint was extended to August 31, 2015. (D.I. 4 and 7/10/2015 Dkt. Notation.) The parties have not yet held a planning conference or filed a joint status report. The Court has not yet held a scheduling conference or issued a scheduling order. No discovery has been requested or taken.

Plaintiffs have filed two other actions against Merck, claiming infringement of two other patents in the same family as the '994 patent. Related case no. 1:14-cv-01131-GMS was filed in September 2014 and concerns U.S. Patent No. 8,728,474. In that case, fact discovery is set to close in February 2016, and trial is set for November 2016. Related case no. 1:15-cv-00560 was filed on June 30, 2015, and concerns U.S. Patent No. 9,067,999. Merck filed a motion to dismiss that action because U.S. Patent No. 9,067,999, like the '994 patent at issue here, is invalid for failure to claim subject matter that is eligible for patent protection.

SUMMARY OF ARGUMENT

1. Section 101 of the Patent Act defines the subject matter eligible for patent protection to be "any new and useful process, machine, manufacture, or composition of matter,

or any new and useful improvement thereof." 35 U.S.C. § 101. "[T]his provision contains an important implicit exception: Laws of nature, natural phenomena, and abstract ideas are not patentable." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014).

2. The Supreme Court in recent years has clarified the boundaries of the exception for natural phenomena, holding that claims that do not include limitations that reflect an inventive contribution beyond a natural phenomenon are unpatentable. *Mayo*, 132 S. Ct. at 1297 (holding that to satisfy § 101, claims directed to "a process that focuses upon the use of a natural law [must] also contain other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself").

3. The Federal Circuit has explained that the *Mayo* test requires the court to assess process claims using a two-step "framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015). "First, we determine whether the claims at issue are directed to a patent-ineligible concept." *Id.* (citing *Mayo*, 132 S. Ct. at 1297). "If the answer is yes, then we next consider the elements of each claim both individually and 'as an ordered combination' to determine whether additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 132 S. Ct. at 1298). "The Supreme Court has described the second step 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.'" *Id.* (quoting *Mayo*, 132 S. Ct. at 1294).

4. Claim 1 – the sole independent claim – reads simply: "A method of treating a metastatic melanoma comprising *intravenously administering an effective amount of a composition comprising a human or humanized anti-PD-1 monoclonal antibody and a solubilizer in a solution* to a human with the metastatic melanoma, wherein the administration of the composition treats the metastatic melanoma in the human." (D.I. 1-1 at clm.1 (emphasis added).)

5. The '994 patent claims do not pass *Mayo*'s two-step test. First, they plainly are directed to a natural phenomenon that occurs in the body – the natural T cell-based immune response against foreign agents regulated by the PD-1 pathway. Second, the patent claims do not transform this natural phenomenon into a patent-eligible invention because they contain no inventive concept. On the contrary, every aspect of this claimed method is admittedly old – administration of antibodies to treat cancer was well known, as were the antibodies being administered here (*i.e.*, antibodies that bind to PD-1). Indeed, as cast, the claims recite *no* features of an anti-PD-1 antibody other than those coextensive with the natural phenomenon itself (*i.e.*, that administration of the antibody "treats the metastatic melanoma" because it induces the natural phenomenon). In other words, the patent claims neither new and inventive agents, nor new and inventive ways of administering known agents; it claims nothing more than causing a natural phenomenon to occur. *See Ariosa*, 788 F.3d at 1378 ("[A]ppending routine, conventional steps to a natural phenomenon, specified at a high level of generality, is not enough to supply an inventive concept."). Because the claims here "are directed to an application that starts and ends with a naturally occurring phenomenon," *id.*, they are invalid for failure to claim patent-eligible subject matter.

6. Rule 12(b)(6) of the Federal Rules of Civil Procedure directs courts to dismiss complaints for "failure to state a claim upon which relief can be granted." To survive a motion to dismiss under Rule 12(b)(6), "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) (internal quotations omitted). Here, the Complaint asserts a claim for infringement of the '994 patent, but the '994 patent is invalid as a matter of law for failure to claim patent-eligible subject matter, so Plaintiffs' patent-infringement claim is not plausible on its face. Courts have invalidated other life sciences patents where the claims were directed to a natural phenomenon or other patent-ineligible subject matter. *See, e.g.*, *Ariosa*, 788 F.3d at 1377 (holding claim to method for detecting paternally inherited DNA from a maternal blood sample to claim patent ineligible subject matter because "the practice of the method claims does not result in an inventive concept that transforms the natural phenomenon of cffDNA into a patentable invention"); *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp.*, 774 F.3d 755, 760–62 (Fed. Cir. 2014) (holding claims to single-stranded DNA primers to be patent ineligible because the primers are not distinguishable from naturally occurring DNA, and holding claims to a method of screening using those DNA primers patent ineligible because the claims "amounted to little more than a broad command to 'apply the law [of nature]'" (brackets in original)). Merck therefore requests that the Court dismiss the Complaint. *See, e.g.*, *Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 713, 717 (Fed. Cir. 2014) (affirming district court's decision granting motion to dismiss under Rule 12(b)(6) because "the district court did not err in holding that the '545 patent does not claim patent-eligible subject matter").

STATEMENT OF FACTS[2]

A. The PD-1 Pathway.

PD-1 is a protein called a "receptor" that is expressed on the surface of activated T cells, which are part of the human immune system. (*See* D.I. 1 at ¶ 4.) Among other immune-system functions, T cells help remove foreign agents – including cancerous cells – from the body. (*Id.*)

The PD-1 receptor serves as a negative immune system "checkpoint." When the PD-1 pathway is activated, it shuts down T cell activity, and thereby suppresses the body's immune response. (*Id.* at ¶¶ 4–5.) When it is not activated, the body's immune response progresses by way of these T cells.

The PD-1 pathway is activated, and the body's immune response is suppressed, when the PD-1 receptor that is expressed on activated T cells binds to one of two other naturally-occurring proteins, called "ligands," which are expressed on other types of cells. These two ligands are PD-L1 and PD-L2. (D.I. 1-1 at col.2:19–45.) In a healthy person, when a T cell with PD-1 on its surface encounters a cell that expresses PD-L1 or PD-L2, the interaction between the ligand and PD-1 activates the PD-1 pathway, which shuts down the activated T cell. (*See* D.I. 1 at ¶ 4.) Thus, the PD-1 pathway prevents T cells from attacking cells that express PD-L1 or PD-L2.

Some cancer cells exploit the PD-1 pathway to escape the body's immune system. They do so by expressing PD-L1 or PD-L2. When T cells with PD-1 on their surface encounter these cancer cells, this triggers the PD-1 pathway on the T cells, thereby shutting down the body's natural immune response against the cancer cells. (*Id.*) The natural operation of the PD-1

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[2] For purposes of deciding a 12(b)(6) motion to dismiss, a court must accept as true all well-pled factual allegations in the complaint. *Iqbal*, 556 U.S. at 678. Accordingly, Merck relies on certain factual allegations in Plaintiffs' Complaint for purposes of this motion but does not concede the truth of Plaintiffs' allegations for any purpose beyond this motion.

pathway and its exploitation by certain cancers was known before the purported invention of the '994 patent. (D.I. 1-1 at col.1–2.)

B. The '994 Patent.

The '994 patent purports to solve this problem by "activat[ing] immunity by inhibiting the inhibitory signals of PD-1, PD-L1 or PD-L2." (D.I. 1-1 at col.2:65–66.) The purported invention proposes to do so by using antibodies that prevent interactions between PD-L1 or PD-L2 and PD-1. (D.I. 1 at ¶ 5.) The '994 patent relies on the known scientific fact that blocking activation of the PD-1 pathway causes this effect in the body, which enables the patient's T cells to perform their normal biological activity of removing cancer cells. (*Id.*) In other words, by preventing PD-1 ligands from binding to the PD-1 receptor, the anti-PD-1 antibodies prevent the PD-1 pathway from suppressing the immune system, which, in turn, kills and clears the body of the "foreign" cancer cells using the body's own natural processes. (D.I. 1-1 at col.2:64–67.)

Anti-PD-1 antibodies which block the interaction of PD-L1 or PD-L2 with PD-1 were known well before the patent was filed. For example, the '994 patent refers to the anti-PD-1 antibody "J43" as an exemplary anti-PD-1 antibody. (*Id.* at col.22:19–30.) This antibody was first disclosed to the public in Yosutoshi Agata *et al.*, "Expression of PD-1 Antigen on the Surface of Stimulated Mouse T and B Lymphocytes," 8 Int'l Immunol. 765-72 (1996) (Ex. 2) (cited in D.I. 1-1 at col.2:5-6 and p.2).[3] Others in the field had also developed anti-PD-1

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[3] When evaluating a motion to dismiss under Fed. R. Civ. P. 12(b)(6), a court may properly consider any "matters incorporated by reference or integral to the claim, items subject to judicial notice, matters of public record, orders [and] items appearing in the record of the case." *Buck v. Hampton Twp. School Dist.*, 452 F.3d 256, 260 (3d Cir. 2006) (citing 5B Charles A. Wright & Arthur R. Miller, *Federal Practice & Procedure* § 1357 (3d ed. 2004)). References cited in the '994 patent prosecution file appear as publically available records in the prosecution history of the patent, which is available on the USPTO Public Patent Application Information Retrieval

antibodies which block the interaction of PD-1 and its ligands. *See, e.g.*, Ex. 3, U.S. Patent No. 6,808,710 at Fig. 26 (showing that PD1-17, a fully human anti-PD-1 antibody, blocks the interaction between PD-L1 and PD-1) (cited in D.I. 1-1 at p.1). The '994 patent likewise acknowledges that techniques for making non-human antibodies suitable for use in human therapy (*i.e.*, humanization) were known and conventional, as were methods for producing fully human anti-PD-1 antibodies. (*See, e.g.*, D.I. 1-1 at col.7:44–45 ("It is possible to make this humanized chimeric antibody expression by a routine method."); *id.* at col.7:46–61 (stating that a "complete human type antibody" can be prepared by conventional methods "using mice" or "by phage display method").)

The '994 patent then purports to claim the natural phenomenon of operation of the body's immune system via the PD-1 pathway. The claims do this by encompassing *all* methods of administering *any* human or humanized anti-PD-1 antibody that induces the body's immune system to do what it does naturally: target and kill cells that are "foreign" to the body, in this case, melanoma cells. Claim 1 (the only independent claim) states:

> A method of treating a metastatic melanoma comprising intravenously administering an effective amount of a composition comprising a human or humanized anti-PD-1 monoclonal antibody and a solubilizer in a solution to a human with the metastatic melanoma, wherein the administration of the composition treats the metastatic melanoma in the human.

(D.I. 1-1 at clm. 1.) The dependent claims add other elements to this method, but all of them are

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(PAIR) website. Plaintiffs have had prior notice of documents which are cited in the '994 patent or which appear in the prosecution file of the '994 patent, and these documents are of indisputable authenticity. *See In re Rockefeller Ctr. Props., Inc. v. Secs. Litig.*, 184 F.3d 280, 293 (3d Cir. 1999) (holding that "all public disclosure documents which are either required to be filed with the SEC or are actually filed with the SEC" and "which relate to or are the basis for the shareholders' complaint" are properly considered as public records).

old and conventional. For example, dependent claim 2 calls for a conventional solubilizer, and claim 3 generically calls for a conventional excipient. (*Id.* at clms. 2–3.) Dependent claims 4–7 require administering the composition in combination with other known anticancer agents. (*Id.* at clms. 4–7.) Dependent claims 8–13 require the antibody to be either humanized or human, which can be made by techniques the '994 patent acknowledges are known and conventional. (*Id.* at clms. 8–13.) Dependent claims 14–24 require the metastatic melanoma to express PD-L1 or PD-L2, and dependent claims 25–30 require such expression to be identified by a conventional technique called immunohistochemistry. (*Id.* at clms. 14–30.) None of the '994 patent claims describes any particular antibody to be used in the claimed methods or specifies any particular attributes of such antibody. They define the antibody entirely by their desired result – *i.e.*, being "effective" to treat "metastatic melanoma in the human." (D.I. 1-1 at clm. 1.) The '994 patent specification provides no further guidance. It broadly defines as "acceptable" those antibodies that "inhibit the immunosuppressive signals by PD-1, PD-L1, or PD-L2," including antibody fragments, antibodies to PD-1, PD-L1, or PD-L2, antibodies from different species (*e.g.*, rabbit, mouse, goat, or human), or even polyclonal antibodies (*i.e.*, a mixture of different antibodies). (D.I. 1-1 at col.5:31–37, col.6:52–54.)

As explained below, because the '994 patent's claim elements were known and conventional, reciting them in the claims cannot transform the natural phenomenon into a patent-eligible method.

ARGUMENT

I. THE '994 PATENT IS INVALID BECAUSE IT CLAIMS SUBJECT MATTER THAT IS NOT ELIGIBLE FOR PATENT PROTECTION.

"Phenomena of nature," even if "just discovered," are "not patentable, as they are the basic tools of scientific and technological work." *Mayo*, 132 S. Ct. at 1293 (quoting *Gottschalk*

v. Benson, 409 U.S. 63, 67 (1972)). The claims of the '994 patent are directed to a natural phenomenon and do not pass the two-step test for patent-eligible subject matter under § 101.

A. The '994 Patent Is Directed To a Known Natural Phenomenon.

The first step of the Section 101 analysis asks "whether the claims at issue are directed to a patent-ineligible concept." *Ariosa*, 788 F.3d at 1375 (citing *Mayo*, 132 S. Ct. at 1297). Here, the answer is yes. The '994 patent claims are directed to the natural phenomenon that occurs in the body when the immune system recognizes cancer cells as foreign, namely, when the PD-1 ligands do not engage the PD-1 receptor, the body's T cells attack the cancer cells as they normally do, but when the ligands to engage, the T cells are shut down.

This is apparent from the results-oriented language of the claims, which specify a single step of "administering an effective amount of a composition comprising anti-PD-1 monoclonal antibody, . . . wherein the *administration of the composition treats the metastatic melonama* in the human." (D.I. 1-1 at clm. 1 (emphasis added).) The specification explains that the mechanism by which the claimed method "treats the metastatic melanoma" is that the antibodies "inhibit the inhibitory signals of PD-1, PD-L1 or PD-L2." (D.I. 1-1 at col.3:8–12.) That is, the cancer is treated not with the antibody that has been administered, but by the natural actions of the immune system functioning in the patient's body, which occur when the PD-1 pathway is not activated (*i.e.*, when it is blocked). *Cf. Ariosa*, 788 F.3d at 1376 (finding that "the claimed method begins and ends with a naturally occurring phenomenon").

B. The Claims of the '994 Patent Contain No Inventive Concept and Therefore Do Not Transform the Claimed Natural Phenomenon Into a Patent-Eligible Application.

The second step of the Section 101 analysis "consider[s] the elements of each claim both individually and 'as an ordered combination' to determine whether additional elements 'transform the nature of the claim' into a patent-eligible application." *Ariosa*, 788 F.3d at 1375 (quoting

Mayo, 132 S. Ct. at 1298). This step is "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.'" *Id.* (quoting *Mayo*, 132 S. Ct. at 1294). The claims of the '994 patent contain no such inventive concept.

"For process claims that encompass [a] natural phenomenon, the process steps are the additional features that must be new and useful." *Ariosa*, 788 F.3d at 1377. Here, the claimed method comprises only a single step – "administering an effective amount of a composition comprising" an admittedly known class of agents, anti-PD-1 antibodies. Researchers had reported administration of immunostimulatory monoclonal antibodies to treat cancer since the mid-1990s. *See, e.g.*, Ex. 4, U.S. Patent No. 5,897,862 (reporting anti-tumor effect of the "immuno-stimulatory" BAT-1 monoclonal antibody) (cited in D.I. 1-1 at p.1); Ex. 5, U.S. Patent No. 6,051,227 (describing administration of an immunostimulatory anti-CTLA-4 monoclonal antibody to treat tumors) (cited in D.I. 1-1 at p.1). Thus the step of administering immunostimulating antibodies to a human to treat cancer is not an inventive concept.

The antibody element of the claims – a human or humanized anti-PD-1 antibody – likewise does not add an inventive concept to the claims. This is because no particular anti-PD-1 antibody is identified; indeed, the claims do not require the antibodies to possess *any* unique properties or capabilities. Rather, the claims cover *any* anti-PD-1 antibody that is effective to "treat[] the metastatic melanoma." (D.I. 1-1 at clm. 1.) That definition of the antibody is entirely circular; it defines the antibodies within the claims as being those which allow the body's natural immune response against cancer cells to progress (*i.e.*, because its T cells are not shut down). Having identified the natural phenomenon, the claim simply calls for the use of *any* anti-PD-1 antibody that induces the natural phenomenon.

The '994 patent acknowledges that, as a class, anti-PD-1 antibodies that prevent PD-1 from binding to PD-L1 or PD-L2 are not inventive. Rather, according to the specification, an "anti-PD-1 monoclonal antibody" as recited in claim 1 "can be manufactured . . . *according to well-known production methods*" and "*well-known protein expression and purification techniques*." (D.I. 1-1 at col.5:38–43 (emphasis added).) The exemplary anti-PD-1 antibody "J43" identified in the patent has been publicly known since the 1990s. *See* Ex. 2, Agata, *supra*, at 765. The only other anti-PD-1 antibody described in the '994 patent, the J110 antibody, was also known in the prior art. *See* Ex. 6, Yoshiko Iwai *et al.*, "Microanatomical Localization of PD-1 in Human Tonsils," 83 Immunol. Lett. 215-20 (2002) (cited in D.I. 1-1 at p.3).[4] Techniques for preparing "human" and "humanized" versions of such antibodies were known as well. (D.I. 1-1 at col.7:28–61.)

That the claims require use of a synthetic agent (here a monoclonal anti-PD-1 antibody) cannot save them. As the Supreme Court has held, the requirement that a known synthetic substance (here, an anti-PD-1 antibody) be administered to a patient to induce a natural reaction does not add an inventive concept to the claims. *See Mayo*, 132 S. Ct. at 1297 ("While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action."). As the Court in *Mayo* explained, "[t]he relation is a consequence of the ways in which thiopurine compounds are metabolized by the body – entirely natural processes." *Id.*

So too here. The administration step of the claimed method triggers an entirely natural process within the body, and the treatment of the cancer by the immune system of the body is a

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[4] *See also* Ex. 7, Pls. Resp. to Merck's Req. for Admis. No. 110, Jul. 1, 2015, *Bristol-Myers Squibb Co. v. Merck & Co., Inc.*, C.A. No. 14-cv-1131-GMS (D. Del.).

consequence of that natural process. The PD-1 pathway – and the immune response that takes place when the ligands PD-L1 and PD-L2 do not bind to PD-1 – exists and operates naturally in the human body, apart from any intervention prescribed by the claims. Because the claims call for triggering this natural process using a conventional synthetic agent in a conventional way, they claim nothing inventive beyond the natural process itself.

The claim language requiring administration "to a human with the metastatic melanoma" also adds nothing to the natural phenomenon; it merely identifies a pre-existing patient population. *See Mayo*, 132 S. Ct. at 1297 ("[T]he 'administering' step simply refers to the relevant audience, namely doctors who treat patients with certain diseases with thiopurine drugs. That audience is a pre-existing audience.").

Likewise, the clause "wherein the administration of the composition treats the metastatic melanoma in the human" merely announces the natural phenomenon, *i.e.*, that the immune response (and thus destruction of cancer cells by T cells) naturally results from administration of an agent that inhibits the natural ligands of PD-1 from triggering the PD-1 pathway. *See Mayo*, 132 S. Ct. at 1297 ("[T]he 'wherein' clauses simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient.").

Finally, claim 1's requirement that the antibody be administered in a "solution" with a "solubilizer" does not add an inventive concept to the claims.[5] Combining active agents and solubilizers in a solution has long been a conventional way of preparing pharmaceutical compositions for use in human treatment. *See, e.g.*, Ex. 8, U.S. Patent Application Pub. No.

[5] Solubilizers and excipients are inactive ingredients used in pharmaceutical compositions to help dissolve active ingredients in water that otherwise dissolve poorly and to make active ingredients more readily available in the body after administration.

2002/0164600 at ¶¶ [0227]–[0238] (cited in D.I. 1-1 at p.2); Ex. 9, U.S. Patent No. 7,858,746 at col.9:60–10:10 (cited in D.I. 1-1 at p.2). As with the anti-PD-1 antibody itself, the claims identify no novel "solubilizers."

The dependent claims do not add anything more than "well-understood, routine, conventional activity already engaged in by the scientific community." *Mayo*, 132 S. Ct. at 1298. Polysorbate 80 (claim 2) was a known solubilizer. *See* Ex. 9, U.S. Patent No. 7,858,746 at col.9:67-10 (cited in D.I. 1-1 at p.1).[6] The use of excipients (claim 3) was also conventional. (*See, e.g.*, D.I. 1-1 at col.13–16 (repeatedly referencing the use of excipients "according to usual methods").) Administering an anticancer agent, such as a chemotherapy drug, in combination with another treatment for cancer in humans (claims 4–7) was a common practice. *See, e.g.*, Ex. 5, U.S. Patent No. 6,051,227 at col.8:41–9:20 ("[U]se of chemotherapeutic agents with CTLA-4 blocking agents . . . increases immunogenicity of irradiated tumor cells. This suggests that the CTLA-4 blockade can be combined with more conventional methods of cancer treatment to produce a synergistic effect.") (cited in D.I. 1-1 at p.1). And others had also proposed combining anti-CTLA-4 antibody therapy with other immunostimulating agents (claims 7). *See, e.g.*, *id.* at col.8:41-64 ("Examples 9 through 12 demonstrate that immune response stimulating agents can have a significant effect on tumor treatment when used in combination with a CTLA-4 blocking agent."). Expression of PD-L1 or PD-L2 by tumors (claims 14–24) had been observed. (D.I. 1-1 at col.2:31–45; *see also* Ex. 11, U.S. Patent No. 7,749,710 at Table 2.) And, finally, immunohistochemistry (claims 25–30) was a well established technique in immunology and had already been reported as a method to detect PD-L1 expressed on human tumor cells. *See* Ex. 11,

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[6] *See also* Ex. 10, Sandeep Nema *et al.*, "Excipients and Their Use in Injectable Products," 51 PDA J. Pharma. Sci. & Tech. 166, 167 (1997) ("Polysorbate 80 is the most common and versatile solubilizing, wetting and emulsifying agent.").

U.S. Patent No. 7,794,710 at col.22:10-62 ("Immunohistochemical analysis demonstrated hB7-H1 [*i.e.*, human PD-L1] expression in a majority of freshly isolated human lung carcinomas (20/21 patients), ovarian carcinomas (20/23 patients), colon carcinomas (10/19 patients) and melanomas (22/22 patients).") (cited in D.I. 1-1 at p.2). As in *Ariosa*, "[t]he dependent claims are focused on the use of the natural phenomenon in combination with well-understood, routine, and conventional activity." 788 F.3d at 1378. The type of conventional activity recited in the '994 patent claims "is normally not sufficient to transform an unpatentable law of nature [or natural phenomenon] into a patent-eligible application." *Mayo*, 132 S. Ct. at 1298.

Considering the '994 patent claim elements as an "ordered combination" also reveals no "inventive concept" that could transform the natural phenomenon into a patent-eligible application. *Mayo*, 132 S. Ct. at 1298. Because the claimed method comprises only a single step, viewing the elements as an "ordered combination" is not meaningfully different from the foregoing analysis of the individual elements. *Cf. id.* (considering three method steps as an ordered combination). Moreover, those elements themselves, alone or in combination, amount to no more than routine, conventional activity or features. *Cf. id.* ("[T]o consider the three steps as an ordered combination adds nothing to the laws of nature that is not already present when the steps are considered separately.").

Plaintiffs may argue that this reasoning would mean that new uses for known compounds are never eligible for patent protection. That contention would be baseless. A patent claiming a new use for a known compound which is appropriately limited to compounds defined in objective terms (*e.g.*, by reference to the structure or physical properties of the molecule) may be patent eligible. The failure of the claims at issue here to define such compounds or to incorporate any other inventive features is what dooms them under Section 101. *Mayo*, 132 S.

Ct. at 1297 ("If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has *additional features* that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself.") (emphasis added). Thus, "[a] claim that recites an abstract idea, law of nature, or natural phenomenon must include '*additional features*' to ensure" that the claim does not monopolize the natural phenomenon. *Ariosa*, 788 F.3d at 1377 (quoting *Mayo*, 132 S. Ct. at 1297) (emphasis added). The claims at issue here contain no additional features, such as structural or physical properties of a particular anti-PD-1 antibody, to differentiate them from the natural phenomenon itself. Because the claims do not specify any particular anti-PD-1 antibody or any particular type or class of anti-PD-1 antibody to be used, they claim the natural phenomenon as such – a building block of the human immune system – and fail to "integrate the building block[] into something more." *Alice*, 134 S. Ct. at 2354 (citing *Mayo*, 312 S. Ct. at 1303 (internal quotation marks omitted)).

To transform a natural phenomenon into a patent-eligible application, a patent must do more than simply recite the phenomenon and add an instruction to apply it. *Mayo*, 132 S. Ct. at 1294, 1297. The '994 patent claims fail this basic test. All they do is provide a general instruction to doctors to use previously known techniques and agents in order to inhibit the immune system's PD-1 pathway in cancer patients. This does not define a patent-eligible method, but instead seeks to patent the natural phenomenon itself. *See, e.g.*, *Ariosa*, 788 F.3d at 1377 (affirming invalidity ruling where "[t]he method at issue here amounts to a general instruction to doctors to apply routine, conventional techniques when seeking to detect cffDNA."). As in *Mayo*, "the combination amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients" where "the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-

understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." 132 S. Ct. at 1298. Here, the claim elements taken individually and as a whole do not convey any inventive contribution and merely instruct doctors to manipulate a natural phenomenon.

It also makes no difference whether, as Plaintiffs assert, the claimed methods represent a "scientific breakthrough" and a "groundbreaking type of cancer treatment." (D.I. 1 at ¶¶ 3, 6.) Even if Plaintiffs had discovered the natural phenomenon that the T cell-based immune response is not suppressed when the ligands of PD-1 do not bind to PD-1 (which they admittedly did not (*see* D.I. 1-1 at col.2:28-31)), and even if this were a groundbreaking discovery, that would not entitle Plaintiffs to patent protection for the natural phenomenon. Similarly, the mouse cancer model described in the '994 patent does no more than allegedly demonstrate the effect of the natural phenomenon of the immune system on cancer cells. (*Id.* at col.25:1–15.) "Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117 (2013). Even if a discovery "may have been a significant contribution to the medical field, that alone does not make it patentable." *Ariosa*, 788 F.3d at 1379–80. Here the purported invention of the '994 patent – the removal of cancer cells from the body – results from a natural phenomenon within the body, and not from any innovative method steps, new composition, or other inventive contribution. Hence, the claimed methods do not define a patent-eligible method. *See id*. at 1380 ("[E]ven such valuable contributions can fall short of statutory patentable subject matter, as it does here.").

II. PLAINTIFFS' COMPLAINT SHOULD BE DISMISSED WITH PREJUDICE BECAUSE THE '994 PATENT IS DIRECTED TO INELIGIBLE SUBJECT MATTER.

Rule 12(b)(6) of the Federal Rules of Civil Procedure directs courts to dismiss complaints for "failure to state a claim upon which relief can be granted." A patent infringement complaint that asserts infringement of claims that are invalid fails to state a claim on which relief can be granted. The claims of the '994 patent fail to claim patent-eligible subject matter. Consequently, Plaintiffs' Complaint does not state a plausible claim for relief and should be dismissed. *See, e.g.*, *Ultramercial*, 772 F.3d at 713, 717 (affirming district court's decision granting pre-answer motion to dismiss under Rule 12(b)(6) because "the district court did not err in holding that the '545 patent does not claim patent-eligible subject matter").[7]

And the dismissal should be with prejudice. Although a plaintiff generally should be given an opportunity to cure pleading defects, that does not apply where "an amendment would be inequitable or futile." *Phillips v. Cnty. of Allegheny*, 515 F.3d 224, 245 (3d Cir. 2008). Any amendment here would be futile, because no amendment can cure the defect that the claims of the '994 patent are invalid as a matter of law. Merck therefore requests that the Court dismiss the Complaint with prejudice. *See, e.g., Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n*, Nos. 12-2501(MAS)(TJB), 12-6960(MAS)(TJB), 2013 WL 3964909, at *1, 14 (D.N.J. July 31, 2013) (granting Rule 12(b)(6) motion because patents in suit "are invalid as

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[7] *See also, e.g., Genetic Techs. Ltd. v. Bristol-Myers Squibb Co.*, 72 F. Supp. 3d 521, 539 (D. Del. 2014) (finding that patent claim directed to natural phenomenon "recites only [patent] ineligible subject matter" and granting motion to dismiss with respect to that claim); *UbiComm, LLC v. Zappos IP*, No. 13-1029-RGA, 2013 WL 6019203, at *6 (D. Del. Nov. 13, 2013) (granting motion to dismiss based on finding that patent claims are invalid under 35 U.S.C. § 101).

abstract ideas not patentable under 35 U.S.C. § 101" and closing the case); *OIP Techs., Inc. v. Amazon.com, Inc.*, No. C-12-1233 EMC, 2012 WL 3985118, at *20 (N.D. Cal. Sept. 11, 2012) ("[T]he Court GRANTS Defendant's motion to dismiss Plaintiff's complaint with prejudice on the grounds that the '713 patent is ineligible under § 101.") (emphasis in original).

CONCLUSION

For the foregoing reasons, Merck respectfully requests that the Court dismiss Plaintiffs' Complaint with prejudice.

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