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,	)	
Plaintiffs,	)	C.A. No. 14-cv-1131-GMS
v.	)	
MERCK & CO., INC. and MERCK SHARP & DOHME CORP.,	)	
Defendants.	)	
BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS, L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO,	)	
Plaintiffs,	)	C.A. No. 15-cv-560-GMS
v.	)	
MERCK & CO., INC. and MERCK SHARP & DOHME CORP.,	)	
Defendants.	)	
BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS, L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO,	)	
Plaintiffs,	)	C.A. No. 15-cv-572-GMS
v.	)	
MERCK & CO., INC. and MERCK SHARP & DOHME CORP.,	)	
Defendants.	)	

PLAINTIFFS' ANSWERING CLAIM CONSTRUCTION BRIEF

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Plaintiffs submit this answering brief in response to the Opening Claim Construction Brief of Defendants Merck & Co., Inc. and Merck Sharp & Dohme Corp. (collectively "Merck") filed on February 25, 2016, and in support of their proposed constructions of disputed terms of the patents-in-suit.

I. INTRODUCTION

Merck's proposed constructions improperly narrow the claim terms and import extraneous limitations. Although Merck pays lip-service to the importance of the plain and ordinary meaning and the intrinsic record when construing terms, its constructions reflect neither. Instead, Merck improperly contorts its constructions to narrow the claims, and props them up with conclusory statements and out-of-context citations to the specification. In the end, those constructions are inconsistent with the specification as a whole and the plain meaning of the claim language. Merck's proposals should therefore be rejected.

II. CONSTRUCTION OF DISPUTED CLAIM TERMS

A. The Treatment/Treating/Treats Terms

The dispute over the terms relating to "treatment" is whether those terms refer to the *attempt* to treat a patient – which is consistent with the plain and ordinary meaning of the terms when read in the context of the patents-in-suit – or whether additional limits related to effectiveness should be imported. As explained in Plaintiffs' Opening Brief, the plain and ordinary meaning of the "treatment" terms is the attempt to treat, with no specific level of efficacy required, and the intrinsic record supports that meaning. *See* Pl. Br. at 6-9 (D.I. 84). Merck's arguments to the contrary are based on a misreading of the specification and should therefore fail.

As an initial matter, Merck's argument, Def. Br. at 7-8 (D.I. 82), that the preamble is limiting for every claim in the three asserted patents is a distraction from the actual dispute about

the proper meaning of the claim terms "treatment" and "treat." The parties have proposed competing constructions for the claim terms, and neither party has argued the language means something different depending on whether or not it is in the preamble. The proper focus of the dispute is on the substantive meaning of "treatment." Both the plain and ordinary meaning and the language of the specification show that Merck proposed the wrong construction.

Merck's argument that a treatment must achieve particular effects or results is inconsistent with the plain meaning in the context of the patents-in-suit. As set forth in detail in Plaintiffs' Opening Brief, the plain and ordinary meaning of "treatment" is "to *attempt* to cause a therapeutic improvement, without necessarily having assurance of what the outcome will be." *Novartis Pharm. Corp. v. Actavis, Inc.*, No. 12-366-RGA-CJB, 2013 U.S. Dist. LEXIS 165317, at *39 (D. Del. Nov. 21, 2013). Thus, while treatment implies the *goal* of achieving results, it does not require the disease to be stopped or slowed in every case. *Schering Corp. v. Mylan Pharm., Inc.*, No. 09-6383, 2011 U.S. Dist. LEXIS 63825, at *16 (D.N.J. June 15, 2011). This interpretation is the sensible one given the reality that treatment is not always effective, especially for a disease as dangerous and complicated as cancer. The fact that a course of cancer treatment does not always achieve results for every patient does not somehow redefine that course as something other than a "treatment." Merck's attempt to redefine the term here should fail.

Importantly, there is nothing in the claim language or the specification that overrides the plain meaning of treatment. Merck argues the fact that claims identify the type of cancer being treated requires a particular effect. Def. Br. at 9 (D.I. 82). But the identification of the type of cancer the claimed method is intended to treat does not support Merck's proposed construction. The ordinary meaning of "treatment" merely requires an attempt to treat the particular type of

cancer identified in each claim. The *goal* is improvement for patients with those cancers, but Merck is wrong to import a requirement for a particular effect.

Merck goes on to incorrectly assert the specification consistently equates "treatment" with suppression of proliferation or metastasis of cancer cells. Def. Br. at 9 (D.I. 82). But Merck's reliance on isolated statements and experimental results in the specification is misplaced because, when viewed as a whole, the specification supports Plaintiffs' construction that "*treating the [tumor, melanoma, lung cancer, or metastastic melanoma]*" is the *potential goal*. The specification does not require this goal be achieved in every case for every patient.

For example, Merck points to the description in the specification of the experimental testing that was done to show that anti-PD-1 antibodies are "substances that inhibit the inhibitory signals of PD-1" that in turn "inhibit cancer proliferation through the mechanism of the recovery and activation of immune function." '474 Patent at 2:62-67 (cited by Def. Br. at 9 (D.I. 82)). The complete description from the specification goes on to say that anti-PD-1 antibodies are "substances that could inhibit the inhibitory signals of PD-1 . . . having *therapeutic potential* for cancer." '474 Patent at 3:2-6 (emphasis added). In another passage, the specification describes that:

> It was suggested that inhibition of PD-1 function or production could achieve an effect similar to the effect on inhibition of PD-Ll function by this antibody. This is based on non-proliferation of imported carcinoma cells in the cancer imported model using PD-1-deficient mice, and presents that inhibition of PD-1 function or production *could be effective on cancer treatment* (Example 5 and FIG. 3).

Id. at 10:60-67 (emphasis added). The experiments in the patents-in-suit did, in fact, demonstrate an effect on proliferation and metastasis in the standard model systems the inventors

used in their testing (as described in detail in the examples in the patents-un-suit).[1] But that does not imply that treatment will always have that particular effect. Again, the goal of treatment is to improve the patient's condition by using anti-PD-1 antibodies – that is the therapeutic potential provided for the first time by the invention here. But that goal does not imply results every time for every patient.

Merck's construction also improperly imports a specific measurement of efficacy – the reduction of proliferation or metastasis – into the construction of the "treatment" terms, but ignores other measurements of efficacy described in the same portions of the specification. In *Gilead Sciences, Inc. v. Abbott Laboratories*, No. 13-2034, 2015 U.S. Dist. LEXIS 148537, at *2, n.1 (D. Del. Nov. 3, 2015), this Court, in addition to finding that "the plain meaning does not support a construction in which the method for measuring effectiveness defines the term treatment itself," refused to adopt a construction that "selects just one of the measures of efficacy discussed in the specification." Similarly, in this case, the specification describes several ways to measure the efficacy of the claimed method of treatment, including "suppression of proliferation, invasion, and metastasis of carcinoma cells, and life prolongation of an individual." '474 Patent at 10:41-65. Merck ignores ways of looking at efficacy, such as "invasion" and "life prolongation," and inexplicably selects "suppression of proliferation . . . [and] metastasis of carcinoma cells" as the only measured effects. Similarly, Merck contends that Example 3 reports that administration of anti-PD-L1 antibodies "suppressed carcinoma cell growth," but Example 3 also evaluates the efficacy of the treatment by measuring the "survival rate of the mice." '474

[1] Contrary to Merck's assertion, the examples in the patents-in-suit describe in detail the effect of blocking PD-1, including through the use of anti-PD-1 antibodies. Def. Br. at 10, n.5 (D.I. 82). This detailed disclosure fully supports the claimed treatment methods.

Patent at 20:13-19. Therefore, Merck's proposed construction should also be rejected because it selectively imports some, but not all, of the measures of efficacy discussed in the specification.

While it appears that both parties rely on their proposed constructions throughout the claims, Merck argues that "[b]y using the active form of the term 'treats'" in the wherein clauses in the body of the claims in the '999 and '994 Patents, the treatment must have a particular effect. Def. Br. at 12 (D.I. 82). But regardless of the form of the verb or its placement in a "wherein" clause, Merck's proposed construction disregards the plain and ordinary meaning of "treatment." For the reasons set forth above, Merck's construction should be rejected.

Finally, Merck improperly implies here, and in other proposed constructions, the focus should be entirely on "cancer cells." Methods of treating cancer are, unfortunately, not able to be so narrowly focused. As Merck's claim construction expert agrees, treatment methods – including surgery, radiation therapy, chemotherapy, and immunotherapy – can affect both cancer cells and the non-cancer cells that are around and intermingled with the cancer cells, von Andrian Dep. Tr. at 55:21-58:2 (Ex. A). The goal of treatment is to get a therapeutic effect for the patient, and treatment methods that have the potential for achieving those effects are directed at the tumor, which contains cancer and non-cancer cells together. Again, Merck's proposal improperly adds limitations to the well-understood concept of "treatment."

In sum, Merck's constructions for the treatment terms should be rejected because they are inconsistent with the plain and ordinary meaning and are not supported by the claims and specification. Contrary to Merck's proposals, "treatment" reflects the attempt to treat, with the goal of achieving therapeutic effect, but that effect need not be achieved for every patient.

B. Pharmaceutically Effective Amount/Effective Amount

Plaintiffs' proposed construction for the "effective amount" terms is consistent with the customary meaning recognized by the Federal Circuit and this Court. *See* Pl. Br. at 10. This

Court has interpreted the Federal Circuit's case law to indicate the customary usage of "effective amount" is "an amount sufficient to achieve the claimed effect." *Merck Sharp & Dohme v. Xellia Pharms, ApS*, No. 14-199-RGA, 2015 U.S. Dist. LEXIS 753, at *9 (D. Del. Jan. 6, 2015) (citing *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1277-78 (Fed. Cir. 2003)). Plaintiffs' proposed construction defines the "claimed effect" as the "pharmacological action of the drug" disclosed in the specification. It is understood in the art that the pharmacological action of a drug is "the proposed mechanism(s) by which a drug achieves its therapeutic effect." George R. Spratto, et al., Preface, in 2013 Edition Delmar Nurse's Drug Handbook 2013, xi (Delmar, Cengage Learning 2013) (Ex. B). The connection between inhibiting the inhibitory signal – in other words, the pharmacological effect – and cancer therapy is described throughout the patents-in-suit. '474 Patent at 1:20-30, 2:58-61, 2:62-67. For example, the patents-in-suit describe compositions for cancer treatment that use anti-PD-1 antibodies to "inhibit the immunosuppressive signals" by PD-1. '474 Patent at 5:22-28. The antibodies that can "inhibit the inhibitory signals" of PD-1 have the "therapeutic potential for cancer . . . ." '474 Patent at 3:2-6. Importantly, the ability to inhibit the inhibitory signal was shown by the inventors through experiments directed specifically to cancer, as described in detail in the examples in the patents-in-suit, *See, e.g.*, '474 Patent at 20:30-55; 24:66-25:11.

Merck is therefore wrong to contend that Plaintiffs' construction is "circular" and "provides no value to the Court or jury." Def. Br. at 12 (D.I. 82). The "pharmacological action" is the mechanism of action of the drug. Ex. B at xi. When the claim language is read in view of the specification, there can be no doubt the effective amount is the amount sufficient to achieve the pharmacologic action of the drug – the inhibition of the inhibitory signal of PD-1. Just like

any other treatment, the amount of an anti-PD-1 antibody that is effective to have that pharmacologic action is something that arises from preclinical and clinical testing.

Merck's proposed construction for "effective amount" improperly tries to rehash the proposal for the "treatment" terms by requiring the reduction of proliferation or metastasis. But there is no basis for this backdoor attempt to require treatment to be achieved in every case. Merck's construction is incorrect because it requires the administration of the drug be effective for every patient. As set forth above, that is the wrong construction for "treatment" – for the same reasons, it is also the wrong construction for "effective amount."

Furthermore, although effectiveness of the treatment for every patient is not required, Merck's construction also fails because it improperly imports some, but not all, of the measurements for assessing the effects of administering an anti-PD-1 antibody that are disclosed in the specification. For example, in addition to reduction of proliferation or metastasis of tumor cells, the specification also discloses that the effectiveness of treatment can be measured by suppression of invasion of carcinoma cells, life prolongation of individuals, survival rate, and tumor volume. *See id.* at 10:53-60, 19:49-52; 20:13-19; Figs. 2(A), 3(B). Merck fails to provide a reason for why these "consequences of administering the anti-PD-1 antibody" are excluded from its construction.

Merck's proposed construction ignores the description in the patents-in-suit of the action of the drug and improperly requires therapeutic effect. That construction should therefore be rejected.

C. Binds to PD-1

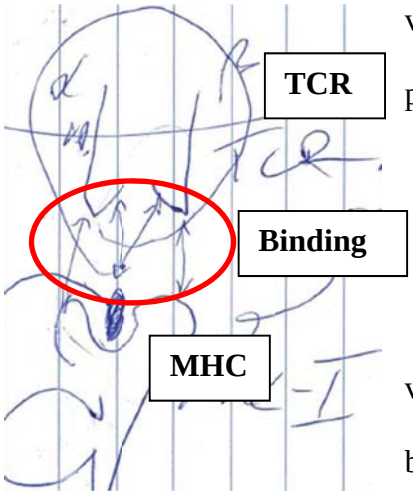
The parties agree that "binds to PD-1" includes forming a direct interaction between the antibody and the PD-1 protein; however, the parties disagree on whether binding also covers *indirect* interactions. Merck's construction, which would encompass such indirect interactions,

is inconsistent with the express disclosures of the patents-in-suit and is scientifically unsound. An antibody that "binds to PD-1" contacts PD-1 directly, not indirectly.

1. The Ordinary Meaning of "Binds to PD-1" Requires a Direct Interaction

Merck's proposed construction of "binds to PD-1" rests on the mistaken premise that "interacts with" and "binds to" can be used interchangeably. But that ignores the plain meaning of "binding."

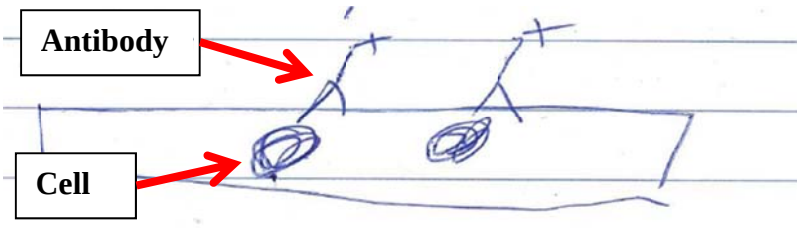
As used in the art, the phrase "binds to" describes a direct interaction. When describing the binding between proteins, Merck's claim construction expert, Dr. von Andrian made clear that binding means the proteins are in *direct* contact. For example, Dr. von Andrian drew the binding between one protein (called the T-cell receptor) and a second protein (called the MHC), and in his drawing the binding (shown by arrows) required direct contact (shown below at left).



von Andrian Dep. at Ex. 6 (Ex. C). In fact, that direct contact is part of what is *meant* by the term binding:

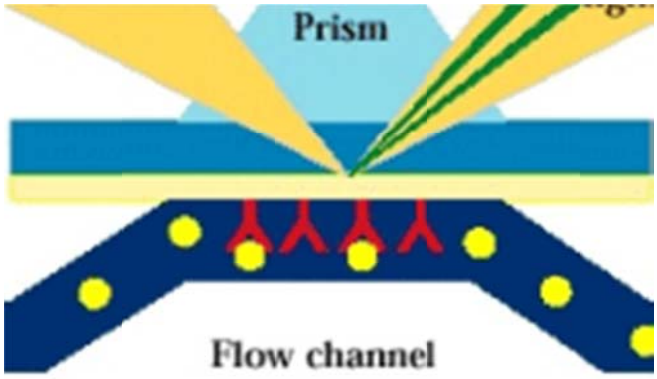
> Q. Is that meant to imply that the T cell receptor is touching the MHC?
>
> A. Yes. That is obviously a part of what's implied when you say binding.

von Andrian Dep. Tr. at 100:9-12. Dr. von Andrian also drew the binding of an antibody to a protein on the surface of a cell, and again, the binding is direct contact between the Y-shaped antibody and the cell (shown below).



von Andrian Dep. at Ex. 8 (Ex. D).

When an antibody "binds to PD-1," as the term is used in the patents-in-suit, chemical bonds form directly between amino acids on the surface of the antibody and amino acids on the surface of PD-1. Charles Janeway, et al, *Antigen Recognition by B-cell and T-cell Receptors*, in Immunobiology 5, Ch. 3, 102-05 (Garland Publishing 2001) (D.I. 84-2). Those chemical bonds are not indirect. Further, it is those chemical bonds that form the antibody-antigen interaction that can be studied using Biacore technology, as described in the Japanese priority application that led to the patents-in-suit. JP 2002-194491, ¶¶ 33-34. Biacore technology is used to determine the affinity of an antibody for its antigen by measuring the binding kinetics of the interaction. As shown in the diagram below, antibodies (shown as red Y-shaped molecules) are immobilized to the surface of a chip. In order for antigen molecules (shown as yellow circles) to bind to the antibodies, they make direct contact with the surface of the antibody, at which point, the Biacore instrument can measure the strength of the interaction between the antibody and the antigen:



https://biophy.uchicago.edu/plasmonresonance.php (last visited Mar. 26, 2016). That is, the Biacore instrument measures direct interactions or binding between antibodies and antigen. Merck's argument that Biacore studies proteins that do not make contact is incorrect as a matter of science.

2. The Specification Uses "Binds to PD-1" to Describe a Direct Interaction

In support of its construction, Merck cites to portions of the specification and prosecution history that describe different ways to inhibit the interaction between PD-1 and its ligands. But the citations Merck provides do not describe direct and indirect *binding*, they describe direct inhibition of the interaction with the PD-1 protein and indirect inhibition of the intracellular signaling of PD-1:

> The immunosuppressive signal of PD-1, PD-L1, or PD-L2 in the present invention is inhibited by direct or indirect inhibition of the interaction of PD-L1 or PD-1 and PD-L2 or the intracellular signaling of PD-1.

'474 Patent at 5:9-12. The distinction between interaction inhibitors and signaling inhibitors is carried through the specification. *See* '474 Patent at 2:67-3:6, 3:21-31, 3:40-47, 3:65-4:6. Plaintiffs do not dispute that inhibition with the signaling pathway can be indirect. But that has nothing to do with *binding* to PD-1, which must be direct.

The specification provides no disclosure indicating that "binds to PD-1," the term before the Court, can somehow include indirect interactions between an antibody and its antigen. Instead, it explains that antibodies that "bind to PD-1" interact with PD-1 directly:

> A substance that *selectively binds to* PD-1, PD-L1, or PD-L2 respectively is included as a substance with those inhibitory activities. For example, it is suitable to be protein, polypeptide or peptide, polynucleotide or polynucleoside, antibody or the derivative, organic synthesis compound, inorganic compound, or natural product. *Especially, an antibody to PD-1, PD-L1 or PD-L2 is enumerated as an excellent substance in specificity*.

'474 Patent at 5:12-19 (emphasis added). In other words, an anti-PD-1 antibody will specifically recognize and selectively bind to PD-1, not other proteins. Because the binding is both selective for and specific to PD-1 and not other proteins, the interaction between an anti-PD-1 antibody and PD-1 must be direct. Otherwise, the antibody would specifically recognize and selectively bind to some other protein. Thus, as used in the specification, the term "binds to PD-1" means to

interact directly with PD-1. Plaintiffs' proposed construction, which accounts for that meaning, is the correct one.

D. Tumor Proliferation

Merck asks the Court to construe "tumor proliferation" in a manner that limits the term to only include an increase in the number of *cancer* cells present in the tumor, rather than an increase in the number of the *total* cells in the tumor. The plain meaning of tumor proliferation is not so limited. Tumors do not proliferate solely because the cancer cells in the tumor are increasing in number. As a tumor proliferates, the cancer cells in the tumor will replicate, *but they must also recruit normal cells that replicate as well*. Pl. Br. at Exhibit C (D.I. 84-3). The end result of this process is an increase in both the number of cancer cells *and* the number of normal cells that are present in the tumor. Merck does not appear to dispute this – it acknowledges that cancer cells "drive the growth of the tumor" and that tumors "typically contain many other types of cells." Def. Br. at 15 (D.I. 82).

The specification further evidences the correctness of Plaintiffs' plain meaning construction. It explains that tumor proliferation can be determined by measuring the size or weight of the tumor, which would inevitably include measurement of both cancer cells and normal cells. *See* '474 Patent at 10:27-31. For example, Figure 4 "shows proliferation suppression of PD-L1 expressing B16 melanomas" as measured by tumor *volume*. '474 Patent at 17:23-25; *see also* Figures 2(A), 3(B), and 5(B) (all using tumor volume as a measure of tumor proliferation). Tumor volume measures the entirety of the tumor, not just the number of cancer cells in the tumor. In other words, the specification discloses that tumor proliferation is a function of an increase in the total number of cells in the tumor, not just the number of cancer cells in the tumor.

Merck ignores the disclosures in the specification that describe "tumor proliferation," and instead focus on the purpose of the claimed method. According to Merck, the purpose of administering anti-PD-1 antibodies is to treat cancer cells. True enough, but that is irrelevant to the meaning of the term "tumor proliferation" because "tumor proliferation" is not defined according to the manner in which it is prevented. Tumor proliferation can be suppressed by killing the cancer cells in the tumor regardless of whether normal cells are present or affected. In fact, most cancer therapies, including immunotherapies such as those claimed in the patents-in-suit, affect both the cancer cells and the normal cells that are present in a tumor. *See* von Andrian Dep. Tr. at 55:21-58:2.

Merck's argument that its construction is correct because it distinguishes between malignant tumors and benign tumors is misplaced. As Merck admits, the specification "makes *crystal clear* that the purpose of administering anti-PD-1 antibodies is to treat cancer cells." Def. Br. at 15-16 (D.I. 82). Because the specification explicitly discloses the methods of the claimed invention are directed to treating cancerous tumors, there can be no confusion as to the purpose or target of the claimed methods. And regardless, the difference between a benign tumor and a malignant tumor is not the proliferation of tumor cells. As Dr. von Andrian explained:

> Q. The tumor cells inside the benign tumor proliferate?
>
> A. Yes.
>
> Q. And the difference between a benign tumor and a malignant tumor is an issue of whether the tumor cells invaded the surrounding tissue; is that right?
>
> Mr. Kushan: Objection; foundation.
>
> A. Whether the tumor cells invade surrounding tissue and shed metastases to discharge, that the two cardinal features of malignant tumors.

von Andrian Dep. Tr. at 151:3-14.

There is no justification for limiting the construction of "tumor proliferation" to an increase in the number of cancer cells. The Court should therefore adopt Plaintiffs' proposed construction, and construe "tumor proliferation" to mean an increase in the number of tumor cells.

E. Tumor Metastasis

The parties' dispute over the construction of tumor metastasis turns on whether tumor metastasis occurs when the cancer cells leave the primary site of disease and move to other parts of the body, as Plaintiffs propose, or whether tumor metastasis further requires development of a secondary tumor away from the primary site of disease, as Merck suggests. Merck's proposed construction improperly narrows the meaning of the term by disregarding the plain meaning of "metastasis" and by misinterpreting the disclosures in the specification.

Merck relies on testimony from Dr. von Andrian who states, based on a textbook by Alberts et al., that tumor metastasis refers to a process whereby cancer cells within a primary tumor move to different locations in the body and create secondary tumors. D.I. 83 at ¶¶ 40-47. But Alberts expressly defines metastasis to mean the "spread of cancer cells from their site of origin to other sites in the body." Bruce Alberts et al., *Glossary*, Molecular Biology of the Cell, (Garland Publishing, 3rd ed. 1994) (Ex. E). Albert's express definition does not require development of a secondary tumor. During his deposition Dr. von Andrian acknowledged that he did not include the glossary section of Alberts in his declaration, von Andrian Dep. Tr. at 39:24-40:10, and that he did not consider any portions of Alberts that were not cited in his declaration. *Id*. at 17:10-18. Instead, Dr. von Andrian selectively cites to *Taber's Medical Dictionary*, but even that text indicates the basic definition of metastasis is "[m]ovement of bacteria or body cells (esp. cancer cells) from one part of the body to another." D.I. 83-11 at 52; *see also* D.I. 83 at ¶ 44. Taber adds in a separate paragraph, the only paragraph cited by Dr. von

Andrian, stating that "the usual application is to the manifestation of a malignancy as a secondary growth arising from the primary growth in a new location." D.I. 83-11 at 52. But that does not change the general meaning of metastasis, which is to move from one area of the body to another.

Merck's construction also rests on a misinterpretation of Example 2 in the patents-in-suit. Figure 2(B) shows staining of images of P815 cells as they move from the primary site of disease to other parts of the body. '474 Patent at 19:59-62. The specification further explains "P815/PD-L1 cells were observed to permeate across the peritoneal cavity and the abdominal cavity, and further those metastases to liver and spleen (FIG. 2(B) a-d)." '474 Patent at 20:1-3. That is, the cancer cells moved across the peritoneal cavity and the abdominal cavity and traveled to the liver and spleen. Nothing in the explanation to Figure 2 requires the development of a secondary growth away from the primary site of disease.

Merck's suggestion that Plaintiffs' construction is imprecise because it uses the term "primary site of disease" is unfounded. Alberts uses a nearly identical designation – "site of origin." There is nothing imprecise about this language. Equally baseless is Merck's assertion that tumor proliferation and tumor metastasis cannot be distinguished under Plaintiffs' constructions. While tumor proliferation and tumor metastasis are related concepts and may occur at the same time, the terms refer to distinct phenomena. Proliferation refers to an increase in the number of tumor cells. Metastasis refers to the movement of the cells away from the primary site of disease to other parts of the body. The terms are not coextensive when construed as Plaintiffs propose. Merck's proposed construction, on the other hand, conflates the terms by requiring proliferation at the secondary tumor site (and the growth of the secondary tumor) as a necessary part of metastasis. Therefore, the Court should adopt Plaintiffs' construction of tumor

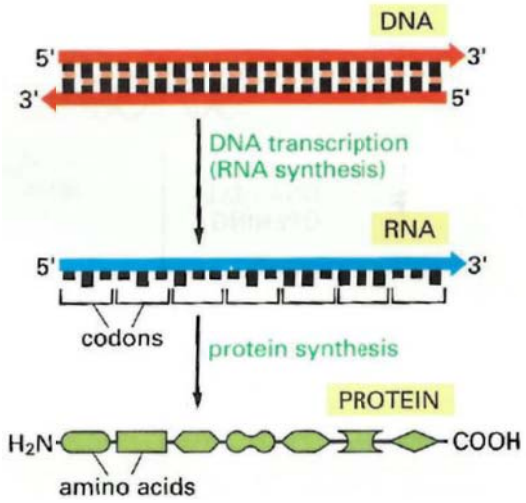
metastasis to mean movement of cancer cells from a primary site of disease to other parts of the body.

F. Expresses/Expression of PD-L1/PD-L2

Merck's proposed construction of the expression terms suffers from multiple flaws. First, Merck improperly narrows the meaning of expression to exclude RNA production even though RNA is widely recognized as a gene product expressed by the cells. Second, Merck proposes, without support or justification, an added requirement that PD-L1/PD-L2 protein production must be at a particular level. Merck's overly restrictive construction contradicts the plain meaning of the terms, as well as their use in the specification. It should therefore be rejected.

1. Expression Includes RNA and Protein Production

The plain meaning of the expression terms is, as Plaintiffs propose, production of a product of the PD-L1/PD-L2 genes. Genes exist in the cells in the form of DNA. *See* Bruce Alberts, et al., *Basic Genetic Mechanisms*, in Molecular Biology of the Cell, Ch. 6, 223 (Garland Publishing, 3 ed. 1994) (Ex. F). In order to be expressed, genes are converted into gene products. Specifically, DNA is converted into RNA, and RNA is converted into protein. *Id.*



(modified image shown above). Both RNA and protein are gene products. This is the central dogma of biology, well known by biologists, including Merck's expert Dr. von Andrian. *See* von Andrian Dep. Tr. at 122:9-123:3.

The plain meaning of the expression terms is further demonstrated by their usage in the specification. The specification unambiguously describes expression of PD-L1/PD-L2 in the context of protein expression, but it also describes expression of PD-L1/PD-L2 in the context of RNA expression. In particular, the specification discloses that PD-L1/PD-L2 expression can be identified by various methods, including: "immunochemical method using PD-L1 antibody or PD-L2 antibody, RT-PCR, or DNA array." '474 Patent at 11:40-42. Immunochemical methods use antibodies to identify the expression of proteins, whereas RT-PCR is a technique that identifies the expression of mRNA. Pl. Br. at Exhibit D (D.I. 84-4); von Andrian Dep. Tr. at 120:8-121:4; 127:20-128:1 In other words, PD-L1/PD-L2 expression can be identified based on the production of RNA or protein, not protein alone as Defendants contend.

Merck argues the expression terms should be limited to the production of only protein (PD-L1 or PD-L2) because some claims in the '999 and '994 Patents specify that expression is identified by immunohistochemistry. As explained above, various methods can be used to identify PD-L1/PD-L2 expression, including methods that identify RNA expression. Immunohistochemistry methods detect protein expression, but that fact only informs the scope of the term immunohistochemistry. Immunohistochemistry, as a separate limitation, cannot be used to narrow the scope of the expression terms. To do so would violate the presumption of claim differentiation. *See GE Lighting Solutions, LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1310 (Fed. Cir. 2014).

Merck also argues that Plaintiffs' construction is confusing because the specification does not use the phrase "product of the PD-L1/PD-L2 gene." Merck again attempts to create confusion by making unfounded assertions about terms that have well-established meanings in the art. The term "gene product" is defined in the art to mean "the biochemical material, either RNA or protein, resulting from expression of a gene." Genetics Home Reference, https://ghr.nlm.nih.gov/glossary=geneproduct (last visited on Mar. 26, 2015) (Ex. G). Similarly, "expression" is regularly used in the art, including in papers authored by Dr. von Andrian, to describe the production of either RNA or protein. *See, e.g.*, von Andrian Dep. at Ex. 9 (Ex. H); *see also* Baron et al., *Distamycin A Inhibits HMGA1-Binding to the P-Selectin Promoter and Attenuates Lung and Liver Inflammation during Murine Endotoxemia*, PLoS One, vol. 5, issue 5, (May 14, 2010) (Ex. I). For example, in a 2003 paper published in the New England Journal of Medicine, Dr. von Andrian used RT-PCR (a technique that measures mRNA levels) to generate "a side by side comparison of FucT -IV and FucT-VII *expression* relative to each other and to 13-actin in each EC population. *See* Ex. H at 1310 (emphasis added); *see also id*. at 1303 (describing the method for "Analysis of FucT Expression by RT-PCR"). In a second paper, Dr. von Andrian again examined expression of a gene product by Northern blotting, a technique that also measures expression of RNA, von Andrian Dep. Tr. at 138:22-24. Ex. I at e10656, page 4 ("To assess the effect of Dist A on inducible *expression of these genes*, lung tissues were harvested from mice at two hours following treatment with Vehicle, LPS/Vehicle, or LPS/Dist A. Tissues were then subjected to RNA extraction and Northern blotting …."). Thus, Plaintiffs propose the expression terms be construed to encompass the production of a gene product – either RNA or proteins corresponding to the PD-L1 or PD-L2 genes – just as the terms are used in the specification and in the art.

Finally, Merck's reliance on Dr. von Andrian's testimony is misplaced. In his declaration, Dr. von Andrian states the expression terms, as used in the claims and specification, should be construed to mean only the production of protein. However, as explained above, the specification describes that expression of PD-L1/L2 can be observed as either RNA expression or protein expression. Thus, Dr. von Andrian's declaration directly contradicts the express disclosures in the specification, and should be discounted. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (en banc) ("a court should discount any expert testimony 'that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent'") (quoting *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998)). Dr. von Andrian's declaration is equally at odds with the use of the expression terms in the art. As evidenced by the references appended to Dr. von Andrian's declaration, the expression terms are used in the art consistent with Plaintiffs' proposed construction – to describe RNA expression, in addition to protein expression. *See* von Andrian Dep. Tr. at 137:5-147:6. Moreover, even if Dr. von Andrian's testimony did not directly contradict both the intrinsic and extrinsic record, his testimony is still deficient because it lacks sufficient foundation to assist the Court. Expert testimony must be supported by independent references, such as industry publications or other independent sources. *Network Commerce, Inc. v. Microsoft Corp.*, 422 F.3d 1353, 1361 (Fed. Cir. 2005). Dr. von Andrian makes several statements interpreting the meaning of the expression terms as they are used in the claims, *see* D.I. 83 ¶ 51 ("[A]s it concerns the meaning in the claims…"), but those statements consist almost entirely of "conclusory, unsupported assertions . . . [that are] 'not useful to a court.'" *Vehicle Interface Techs., LLC v. Ford Motor Co.*, C.A. No.

12-1284-RGA, 2015 U.S. Dist. LEXIS 6576, at *11 (D. Del. Jan. 21, 2015) (quoting *Phillips*, 415 F.3d at 1317).

2. The Expression Terms Do Not Require Detection

Merck offers no explanation for why PD-L1/PD-L2 expression should be construed to include the added limitation of detectability of particular levels of protein. The detectability requirement fails to comport with the plain meaning of the expression terms or the use of the terms in the specification, both of which require only that a product of the PD-L1/PD-L2 gene be produced. Again, expression is properly understood as the production of RNA or protein, and the specification describes a variety of methods available to determine whether that production has occurred. '474 Patent at 11:40-42. Merck's attempt to require protein to be produced in a particular amount is inconsistent with that variety of methods, and Merck's proposed construction should be rejected.

III. CONCLUSION

Plaintiffs respectfully request the Court adopt their proposed claim constructions.

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Respectfully submitted,

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