UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case PGR-Unassigned

U.S. Patent No. 10,611,836

PETITION FOR POST GRANT REVIEW
UNDER 35 U.S.C. §§ 321-329 AND 37 C.F.R. § 42.200

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1003	Expert Declaration of James McDonnell, Ph.D.
1004	File History for U.S. Patent No. 10,611,836 (2 Volumes)
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I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Merck") respectfully requests institution of a post-grant review ("PGR") of claims 1 and 3-12 (the "Challenged Claims") of U.S. Patent No. 10,611,836 ("the '836 patent") pursuant to 35 U.S.C. §§ 321-329 and 37 C.F.R. § 42.200 et seq.

The '836 patent, assigned to Genentech, Inc. ("Genentech"), claims, *inter alia*, methods of treating or delaying progression of a cancer or increasing, enhancing, or stimulating an immune response or function in an individual by co-administering a PD-1 axis binding antagonist and an inhibitory anti-TIGIT antibody. The claims are breathtakingly broad. They cover any anti-TIGIT antibody and any PD-1 axis binding antagonist that meet the functional definitions set forth in the claims, and the claims cover treating any and all types of cancer in an "individual," which includes humans and other mammals.

Despite the breadth of the claims, the specification contains shockingly little disclosure. It discloses only a single anti-TIGIT antibody that meets the functional limitations of the claims and only eight examples of the claimed PD-1 axis binding antagonists, which can include both antibodies and other types of molecules, e.g., fusion proteins. And the specification only provides test data treating mice in two types of cancer with only one anti-TIGIT and one anti-PD-L1 antibody. Because the patent specification lacks sufficient disclosure both to show possession of the

broadly claimed invention and to enable a person of ordinary skill in the art ("POSA") to practice the full claim scope, the claims are invalid under 35 U.S.C. § 112.

More specifically, the specification does not provide a sufficient description that would allow a POSA to recognize or visualize the full scope of the broadly claimed genera of anti-TIGIT antibodies and PD-1 axis binding antagonists. Likewise, the data in the specification showing that the claimed method can treat two types of tumors in mice does not demonstrate that the inventors were in possession of a method that can be used to treat any and all types of cancer in any individual, including humans.

Similarly, the lack of disclosure in the specification means that a POSA would need to engage in undue experimentation to practice the full scope of the claims. Indeed, simply making and screening the full scope of the claimed anti-TIGIT antibodies and PD-1 axis binding antagonists would require the exact type of trial-and-error testing that the case law rejects. But even after making and testing the claimed anti-TIGIT antibodies and PD-1 axis binding antagonists, a POSA would still need to determine the "effective amount" of each of these compounds and test their efficacy in treating any and all types of cancer.

Finally, the Challenged Claims are invalid under 35 U.S.C. § 103. The prior art Gao reference, not cited by the Examiner during examination, provides an

explicit teaching that TIGIT antagonists, including blocking anti-TIGIT antibodies, can be synergistically co-administered with other immune checkpoint inhibitors, including in particular, the PD-1 axis. A POSA thus would have had a strong motivation to simultaneously block TIGIT and PD-1 and would have been motivated to select known anti-TIGIT and anti-PD-L1 antibodies to treat cancer synergistically.

Moreover, any attempt to rely on the alleged synergistic results as an unexpected property to rebut obviousness would fail here for the additional reason that the demonstration of any such results is not even close to being commensurate in scope with the broad claims in the ’836 patent. The experimental animal model results involved one PD-1 axis binding antagonist combined with one anti-TIGIT antagonist against one type of viral infection and two types of cancer. In contrast, the incredibly broad claims cover all types of anti-TIGIT antibodies, all types of PD-1 axis binding antagonists, and all types of cancers.

Accordingly, Merck respectfully requests institution of a PGR on claims 1 and 3-12 of the ’836 patent.

II. MANDATORY NOTICES

As set forth below and pursuant to 37 C.F.R. § 42.8(a)(1), the following mandatory notices are provided as part of this petition.

A. Real Parties in Interest (37 C.F.R. § 42.8(b)(1))

Merck is the real party-in-interest.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

The ’836 patent issued on April 7, 2020 from underlying U.S. Application No. 15/239,569, filed on August 17, 2016 (“the ’569 application”). The ’569 Application is a divisional of U.S. Application No. 14/333,375 (“the ’375 application”), filed on July 16, 2014. According to the USPTO’s Patent Application Information Retrieval system, one unpublished application claiming priority to the ’375 application is pending before the USPTO: U.S. Application No. 16/818,820, filed on March 13, 2020.

C. Lead and Backup Counsel (37 C.F.R. §§ 42.8(b)(3) & 42.10(a))

Petitioner hereby designates lead and backup counsel as follows:

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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please send all correspondence to the lead and backup counsel at the addresses shown above. Petitioner consents to service by e-mail at the addresses of lead and back-up counsel shown above.

E. Payment of Fees (37 C.F.R. §§ 42.203 and 42.15(b))

The requisite filing fee of $47,500 (request fee of $20,000, post-institution fee of $27,500) for a Petition for PGR is submitted herewith. Claims 1 and 3-12 of the ’836 patent are being reviewed as part of this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 505708. Any overpayment or refund of fees may also be deposited in this Deposit Account.

III. ADDITIONAL REQUIREMENTS FOR POST-GRANT REVIEW

A. Grounds for Standing (37 C.F.R. § 42.204(a))

Petitioner certifies that the ’836 patent is available for PGR and that Petitioner is not barred or estopped from requesting PGR on the grounds identified in this Petition. Specifically: (1) neither Petitioner nor any of its privies own the ’836 patent; and (2) neither Petitioner nor any of its privies have filed a U.S. civil action challenging the validity of any claim of the ’836 patent.

The earliest possible effective filing date for the ’836 patent is July 16, 2013, the filing date of the first provisional application (serial no. 61/846,941). Thus, the ’836 patent is subject to AIA and eligible for PGR.

B. Time for Filing Petition

The ’836 patent issued on April 7, 2020, and the instant Petition was timely filed no later than the date that is nine months after the date of the grant of that patent.

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED (37 C.F.R. § 42.204(B) & 37 C.F.R. § 42.22(A)(1))

The precise relief requested by Petitioner is that claims 1 and 3-12 (the “Challenged Claims”) are found unpatentable and cancelled from the ’836 patent.

A. Claims for which Post-Grant Review is Requested (37 C.F.R. § 42.204(b)(2))

Petitioner requests PGR of the claims 1 and 3-12 of the ’836 patent.

B. Specific Statutory Grounds on which the Challenge is Based (37 C.F.R. § 42.204(b)(2))

The specific statutory grounds for the challenge are as follows:

Ground 1:	Claims 1 and 3-12 are invalid under 35 U.S.C. § 112(a) for lack of written description.
Ground 2:	Claims 1 and 3-12 are invalid under 35 U.S.C. § 112(a) for lack of enablement.
Ground 3:	Claims 1 and 3-12 are obvious under 35 U.S.C. § 103(a) over Gao in view of Clark and Irving.

V. THE ’836 PATENT

A. Summary of the ’836 Patent

The ’836 patent issued from the ’569 application, filed on August 17, 2016, which is a divisional application of U.S. Application No. 14/333,375, filed on July 16, 2014 (Ex. 1005). The ’836 patent claims priority to five provisional applications: No. 61/846,941, filed on July 16, 2013 (Ex. 1006); No. 61/865,582, filed on August 13, 2013 (Ex. 1007); No. 61/950,754, filed on March 10, 2014 (Ex. 1008); No. 61/985,884, filed on April 29, 2014 (Ex. 1009); and No. 61/992,109, filed on May 12, 2014 (Ex. 1010).

The Challenged Claims are directed to methods of treating or delaying progression of a cancer and, more generally, methods of stimulating an immune response. Each claimed method requires co-administration of two previously known classes of compounds—PD-1 axis binding antagonists and anti-TIGIT antibodies.

The ’836 patent inventors do not purport to have discovered either class of compounds or to have discovered their efficacy in treating cancers or their role in stimulating an immune response. Rather, the inventors co-administered one compound from each class and then measured the resulting efficacy from the combination. The ’836 patent states that the combination in that example achieved synergistic results in two types of cancer in mice.

The Challenged Claims are not limited to the combination of the specific PD-1 axis binding antagonist and the specific anti-TIGIT antibody that allegedly achieved the purported synergy for two types of cancer in mice. Rather, these claims are directed to the combination of a broad genus of PD-1 axis binding antagonists and a broad genus of inhibitory anti-TIGIT antibodies for treating any and all possible forms of cancers. For example, independent claim 1[1] recites:

> 1. A method of ***treating or delaying progression of a cancer*** in an individual, the method comprising administering to the individual an effective amount of (i) a ***PD-L1 binding antagonist*** that inhibits the binding of

[1] Claim 3, the only other independent claim being challenged, is nearly identical to claim 1, differing only in the preamble which specifies “[a] method of increasing, enhancing, or stimulating an immune response or function in an individual.” Ex. 1001, 136:57-67.

> PD-L1 to PD-1 and/or B7-1, ***a PD-1 binding antagonist*** that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or ***a PD-L2 binding antagonist*** that inhibits the binding of PD-L2 to PD-1 and (ii) an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is ***an inhibitory anti-TIGIT antibody*** or antigen-binding fragment thereof.

Ex. 1001, 135:52-62.[2] The first element of this claim is "treating or delaying progression of a cancer." The '836 patent specification defines "cancer" as "the physiological condition in mammals that is typically characterized by unregulated cell growth," and broadly includes "benign and malignant cancers as well as dormant tumors or micrometastatses." *Id.* 53:1-5. The '836 patent lists over 40 exemplary cancers and dependent claim 10 narrows the broad recitation of "cancer" to 25 different cancers. *Id.* 53:5-31, 138:4-13.

The second element of the claim is the administration of a PD-1 axis binding antagonist, which is defined in the broadest possible functional manner. The claim describes three sub-genera of binding antagonists (directed PD-L1, PD-1, or PD-L2), with no recitation of structure, but instead based solely on the ability to inhibit binding in the PD-1 signaling pathways:

- "a ***PD-L1 binding antagonist*** that inhibits the binding of PD-L1 to PD-1 and/or B7-1,"

[2] Throughout this Petition, all emphases are added unless otherwise noted.

- "a ***PD-1 binding antagonist*** that inhibits the binding of PD-1 to PD-L1 and/or PD-L2," **<u>or</u>**
- "a ***PD-L2 binding antagonist*** that inhibits the binding of PD-L2 to PD-1"

Id. 135:54-59. The scope of each sub-genera is not limited to the countless antibodies that might perform these functions. Rather, the specification makes clear that this claim element encompasses any molecule that inhibits the specified binding pathway, including immunoadhesins, fusion proteins, oligopeptides, and small molecules. *Id.* at 39:36-42, 39:62-40:2, 40:22-28. In contrast to the broad genus recited in the claims, the '836 patent specification specifically discloses only eight PD-1 axis binding antagonists: three anti-PD-1 antibodies (MDX-1106, Merck 3745, and CT-011), four anti-PD-L1 antibodies (25A1, MPDL3280A/YW243.55.S70, MDX-1105, and MEDI 4736), and one immunoadhesin (AMP-224). *Id.* 63:60-66, 101:53-63.

The third element of the claim is the administration of an agent that "inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof." *Id.* 135:59-62. Thus, the claim element requires two functions. First, the agent must be "an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof," *id.* 135:61, which means that the agent must inhibit the biological activity of TIGIT, such as by binding to the TIGIT protein. Second, the agent must inhibit and/or block the

interaction of CD226 with TIGIT. *Id.* 135:59-60. The '836 patent specification discloses only one antibody with these two functions—clone 10A7. Ex. 1001, 98:51-100:31, 107:40-106:59.

B. Examination of the '836 Patent

As noted above, the '836 patent issued from the '569 application. The original claims of the '569 application were directed to, *inter alia*, methods of treatment by administering "an effective amount of a PD-1 axis binding antagonist," an "agent that decreases or inhibits TIGIT expression and/or activity" (e.g., claim 1), or an "agent that decreases or inhibits CD226 expression and/or activity" (e.g., claim 6). Ex. 1004 at 221.

On November 5, 2018, the Patent Examiner issued a restriction requirement. In response, Genentech elected claims directed to the co-administration of a "PD-1 axis binding antagonist and an agent that inhibits and/or blocks the interaction of CD226 with TIGIT." Ex. 1004 at 598, 608. At the same time, Genentech amended the elected claims to require an agent that "inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof." *Id.* at 605.

On June 18, 2019, the Patent Examiner issued a non-final office action rejecting all pending claims. *Id.* at 335. The grounds for rejection included indefiniteness, non-enablement, obviousness over the prior art, and obviousness-

type double patenting. For the obviousness rejection, the Examiner relied on Maecker et al. (US 2014/0341902) in view of Clark et al. (US 2009/0258013). *Id.* at 617.

The Examiner relied on Maecker as teaching "the inhibition of PD-1 axis signaling through its direct ligands PD-L1 and PD-L2" as a "means to enhance anti-tumor T cell immunity for the treatment of cancer." *Id.* The Examiner cited Clark as teaching that anti-TIGIT antagonists are useful for the treatment of immune-related diseases by blocking "TIGIT-induced inhibition of T cell proliferation." *Id.* at 619. The Examiner further cited Clark as providing two working examples of anti-TIGIT antibodies 10A7 and 1F4—the same two anti-TIGIT antibodies identified in the specification of the '836 patent. *Id.*

For motivation to combine the references, the Examiner relied on Maecker's teaching that "an optimal cancer treatment would combine blockade of PD-1 receptor/ligand interaction with a ***second agent that contributes additional immune enhancing properties*** not provided by PD-1 blockade alone." *Id.* at 1988. The Examiner noted, however, that Maecker "***does not specifically exemplify a TIGIT antagonist as the second agent***." *Id.* at 620. While Maecker did not specifically identify TIGIT antagonists as the second agent, the Examiner found that Clark taught that anti-TIGIT antagonists that would contribute "additional immune enhancing properties not provided by PD-1 blockade alone," as called out in Maecker. *Id.*

Further, a POSA "would have a reasonable expectation of success, because both PD-1 signaling blockade and TIGIT signaling blockade are taught to be useful in cancer treatment." *Id.*

In response to the obviousness rejection, Genentech argued that combining PD-1 axis binding antagonists with anti-TIGIT antagonists resulted in "***unexpected synergy*** in treating or delaying progression of viral infection or cancer in reliable animal models." *Id.* at 642. Genentech cited Examples 3 and 5, which they indicated involved combining one PD-1 axis binding antagonist with one anti-TIGIT antagonist to test for reduction in one type of viral infection and one type of cancer. *Id.* at 642-43. Genentech further argued that the prior art did not "suggest this synergy exhibited by the present invention." Rather, according to Genentech, the synergistic result was completely unexpected:

> Specifically, it was unexpectedly found by Applicant that the particular combination of agents, which had modest or no efficacy when administered as monotherapies, could synergize to dramatically treat or delay the progression of cancers …. Such synergy represents an unexpected result and is persuasive evidence of the non-obviousness of the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Id. at 642.

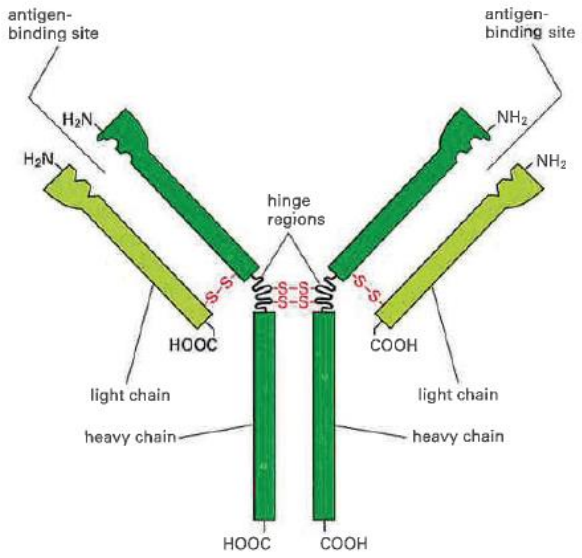
Following this response, the claims were allowed. In the reasons for allowance, the Examiner stated that "the state of the art at the time of the effective filing date of the present invention was insufficiently predictable to provide a reasonable expectation that the claimed combination of agents would have a synergistic therapeutic effect." *Id.* at 653. At that time, however, the Examiner was not aware of the prior art teaching of Gao explicitly stating that anti-TIGIT agents could be combined with anti-PD-1 agents.

VI. THE STATE OF THE ART

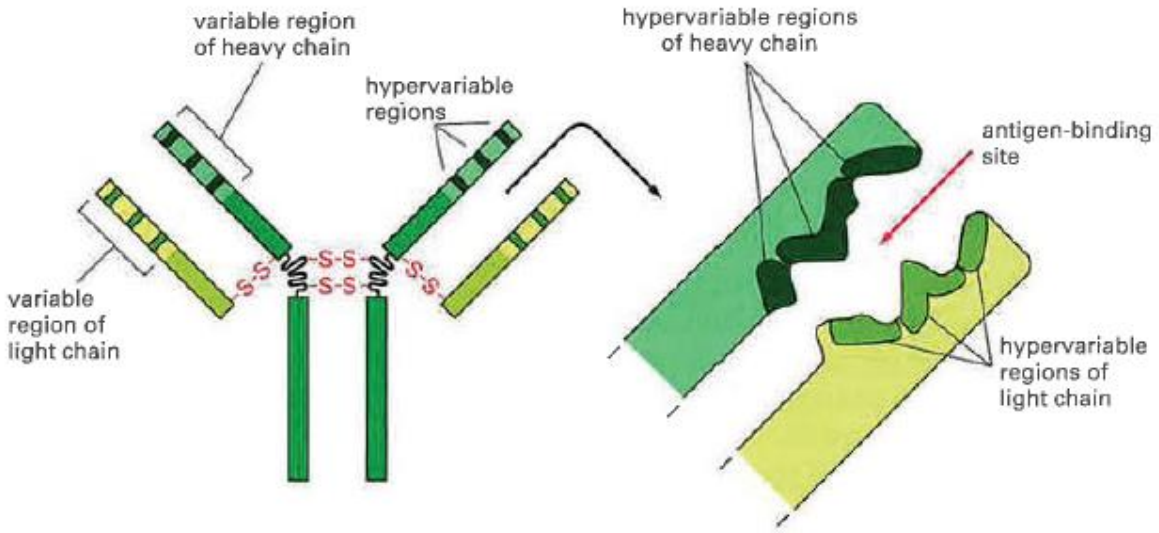
A. Antibodies

1. Antibody Structure

An antibody is a protein that specifically binds to a target called an antigen. Ex. 1012 at 1364, 1369. Antibodies are produced naturally in response to invading foreign molecules, including those from or on cancer cells. *Id.* Antibodies typically comprise four amino acid chains—two identical "heavy chains" and two identical "light chains"—that pair to form a "Y" shape, *id.*:



Ex. 1012 at 1377, Fig. 24-21. The heavy and light chains each have a "constant" domain or region and a "variable" domain or region. *Id.* at 1381-82, Fig. 24-31. The variable domains are located on the "arms" of the Y-shaped antibody, while the constant domain is located at the "base" of the Y. *Id.* The variable domains are responsible for binding an antigen while the constant domain contributes to other functions in the body. *Id.* at 1382-84. Each variable region contains three complementarity determining regions ("CDRs"), also known as hypervariable regions:



Id. at 1382, Fig. 24-31. Variants of this general structure are known, as well as antibody fragments, such as Fab fragments, that retain the components of the variable region, e.g., the CDRs, needed to bind an antigen. Ex. 1013 at 143; Ex. 1014 at 5879, 5882-83; Ex. 1016 at 96.

2. Antibody Function

The region of an antigen that interacts with an antibody is called the epitope. *Id.*; Ex. 1015 at 81; Ex. 1016 at 102. A given antibody binds to a specific epitope, but there can be multiple epitopes on each antigen. *Id.*; Ex. 1016 at 102-03; Ex. 1017 at 14, 15-16. The epitope to which an antibody specifically binds is a determinant of the antibody's function. Ex. 1002 ¶50; Ex. 1012 at 1376. Therapeutic antibodies, for example, may serve either an agonist or antagonist function depending on where they bind. *Id.* ¶51. Agonist antibodies mimic the binding of a receptor to its natural ligand, producing an intracellular signal and a biological

response. *Id.* Antagonist antibodies block the binding of the receptor to its ligand and inhibit signaling. *Id.* Some therapeutic antibodies can also bind to an epitope outside of the functional region of the antigen. *Id.* ¶52. Because antibodies to a given antigen can bind to any number of epitopes on the surface of that antigen, it is not possible, prior to testing, to determine which epitope a newly-isolated antibody will bind to, and thus what function it will have. *Id.* ¶54; Ex. 1018 at 118-19; Ex. 1019 at 15; Ex. 1020 at 242-45; Ex. 1020 at 227; Ex. 1021 at Abstract.

3. Antibody Variability

Antibodies can have vastly different amino acid sequences. Ex. 1002 ¶55. The total number of antibody specificities available to an individual is known as the antibody repertoire, or immunoglobulin repertoire, and in humans the current estimate is as high as 10^{12} based on theoretical combinatorial calculations. *Id.*; Ex. 1013 at 124, 131-36, 138; Ex. 1016 at 93,101. This variability allows different antibodies to bind to a wide range of different target antigens and different epitopes within target antigens. Ex. 1002 ¶56. Significant diversity occurs in the variable regions of the antibodies, particularly in the regions referred to as CDRs because they directly interact with a target antigen. *Id.* ¶57; Ex. 1016 at 93, 96, 101-03. Each of the heavy and light chains contains three CDRs in its variable domain for a total of six CDRs on each arm of an antibody. Ex. 1002 ¶56. Those six CDRs interact to

form the antigen-binding pocket, and all six CDRs typically contribute to determining which antigen an antibody will bind. *Id.*

The structure of the binding pocket formed by the CDRs is also maintained by four framework regions ("FRs") on each of the heavy and light chains. *Id.* ¶57; Ex. 1016 at 101-02. These FRs surround the CDRs, contribute to the shape and stability of the binding pocket that contacts a target antigen, and also provide additional sequence diversity. *Id.* The binding pocket comprising the CDRs provides the main determinant of what antigen an antibody will bind. *Id.* Even minor variations anywhere in the variable region, and particularly in the CDRs, can alter the structure of the binding pocket, affecting the affinity with which an antibody binds its target antigen. *Id.*

Given this extensive variability among antibodies, different antibody sequences may bind to the same or similar epitopes, while at the same time antibodies with similar sequences can form three-dimensional structures that bind different antigens. *Id.* ¶58. And because differences in sequence not only affect antigen specificity and affinity for that antigen, but also dictate functional consequences in biologic systems, it is difficult to predict before testing which antibody sequences will bind a chosen antigen, where on the antigen the antibody will bind, and the biologic effect the antibody will have. *Id.* ¶59.

4. Development of Therapeutic Antibodies

Antibodies can be generated in a number of different ways. *Id.* ¶60. Intentionally exposing an animal to an antigen to induce an immune response, i.e., to produce antibodies, is one technique employed to generate a library of potential antibody leads and is referred to as "immunization." *Id.*; Ex. 1018 at 122. As mentioned above, human immune cells have a repertoire of 10^{12} unique sequences from which antibodies that bind to a target antigen are selected. Ex. 1002 ¶60; Ex. 1013 at 124, 138; *see* Ex. 1012 at 1385.

As an alternative to immunizing an animal to prepare antibodies, many companies maintain large libraries of murine or human antibody sequences, or fragments of such antibodies, isolated from naive murine or human B cells that can be screened for desired antigen binding. Ex. 1002 ¶61; Ex. 1018 at 124-25. Phage display involves the insertion of different genes encoding antibody variable domains into bacteriophage, which is a type of virus that infects bacteria. *Id.* ¶62. The bacteriophage express the antibody genes and present the resulting antibody segments on their coat protein, thereby "displaying" the antibody sequences, which are then screened to select for antibodies with desired properties, e.g., binding and function. *Id.*; Ex. 1022 at 725-26; Ex. 1023 at 4133, 4136-37; Ex. 1024 at 581, 594; Ex. 1025 at 189-90; Ex. 1026 at 309, 311-13. Regardless of whether antibody screening is accomplished via phage display or the immunization method described

above, extensive additional work and engineering may be needed to further optimize and refine an antibody for therapeutic use. Ex. 1002 ¶63.

Moreover, because of the unpredictability and variability discussed above, one of ordinary skill in the art would need to screen numerous candidate antibodies having vastly different sequences and structures to identify and characterize monoclonal antibodies with the desired properties. *Id.* ¶64. Prior to screening, there is no definitive way to predict whether an antibody is capable of binding a specific antigen, is suitable for administration to a human, or has a desired therapeutic effect. *Id.* ¶65.

B. Cancer Immunotherapy

1. Background on Cancer

Cancer is a complex set of diseases caused by the abnormal, unregulated growth of cells. *Id.* ¶66. Abnormal, unregulated growth can develop in tissues when an injured or aberrant cell does not follow the natural process of cell death, and the cell is able to reproduce in an uncontrolled manner. *Id.*

There are many different kinds of cancers, including carcinomas, sarcomas, lymphomas, leukemias, and germ cell tumors. *Id.* ¶67. A common type of cancer is carcinoma, which is a class of cancer occurring in the epithelium—skin, glands, or other lining elements and organs in our bodies. *Id.*; Ex. 1027 at 284, 295-98. Breast cancer, lung cancer, and prostate cancer are each categorized as carcinomas,

but they are very different diseases based in part on the different characteristics of the tissue where the cancer is located. Ex. 1002 ¶67. Even within each tissue type, many different subtypes can occur, each displaying a specific morphology, sub-type treatment plan, and prognosis. *Id.* In addition, there are innumerable complexities, including inter- and intra-individual heterogeneity of particular cancer subtypes. *Id.*; Ex. 1028 at 333. The granularity of cancer typing is evidence of the diverse nature of cancer. Ex. 1002 ¶67.

Because the types of cancers and ways in which they develop are so varied, each cancer type requires a different treatment approach. *Id.* ¶68. For example, cancer therapy can involve radiation, surgery, and/or chemical or biological agents. *Id.* One class of cancer therapy is termed "cancer immunotherapy," which refers broadly to cancer treatments that use the human body's own immune system to find and destroy cancer cells. *Id.* ¶72; Ex. 1029 at 252. Unlike conventional treatments (such as surgery, chemotherapy, and radiation), immunotherapy provides a targeted approach to cancer treatment. Ex. 1002 ¶72. One approach in cancer immunotherapy is to utilize therapeutic antibodies to block what are termed "immune checkpoints." *Id.*

2. Immune Checkpoint Inhibitors

Immune checkpoints are natural molecular pathways used to regulate the immune system by preventing the immune system from attacking cells

indiscriminately. *Id.* ¶73. Tumors co-opt certain immune-checkpoint pathways as a mechanism of immune evasion, particularly evading T cells that are specific for tumor antigens. *Id.* T cells are a type of white blood cell that play a central role in cell-mediated immunity. *Id.* They have a receptor on their surface called a T cell receptor. *Id.* This T cell receptor is important in the function of T cells because of the receptor's ability to scan the body for foreign antigens (e.g., bacteria or viruses) or tumor cells. *Id.* To perform that function, T cells must be able to distinguish between normal, healthy cells, on the one hand, and foreign invaders and cancer cells, on the other hand. *Id.* Tumor cells are derived from normal, healthy cells in the patient, and they can evade T cells because they present self-proteins that prevent tumor cells from being recognized by T cells, and therefore prevent T cell activation and the resulting cytotoxicity. *Id.* Immune checkpoint inhibitors—for instance, blocking antibodies—work to allow the immune system to mount an attack against tumor cells through stimulation of T cell activation. *Id.* The result is to remove the block that prevented T cells from recognizing the cells as cancerous, thus leading to an immune response to the cancer cells. *Id.*; Ex. 1029 at 253.

There are many immune checkpoint proteins that have been and are still being discovered. These immune checkpoint proteins include, among others, PD-1 and TIGIT. Ex. 1002 ¶74.

(a) PD-1

One of the most well-studied immune checkpoints receptors is programmed cell death protein 1 ("PD-1"). *Id.* ¶75. PD-1 is a member of the CD28 family of immune checkpoint receptors. *Id.*; Ex. 1029 at 256-57. The CD28 family of receptors are critical determinants of the outcome of T cell activation. Ex. 1002 ¶75. These receptors interact with ligands in the B7 family to either stimulate or inhibit T cell responses. *Id.* For example, CD28 is a stimulatory receptor. CD28 binds with either the B7-1 or B7-2 ligand and delivers a positive signal that stimulates (or "upregulates") T cell responses, i.e., increases the immune response so as to kill a pathogen. *Id.* By contrast, PD-1 is an inhibitory receptor whose signal downregulates the immune response. *Id.*

The major role of the PD-1 pathway is not at the initial T cell activation stage. Rather, PD-1 regulates inflammatory responses in tissues by effector T cells that have recognized an antigen in peripheral tissues. *Id.* ¶76. After antigen receptor activation, T cells synthesize and display on their surface a number of new receptors, including PD-1. *Id.* PD-1 has two known ligands: PD-L1 and PD-L2. *Id.* When PD-L1 or PD-L2 expressed on normal cells bind to PD-1 expressed on activated T cells, the effect is to inhibit (or "downregulate") T cell activity. *Id.* In this way, the PD-1/PD-L interaction prevents T cells from launching an immune response against an individual's normal cells. *Id.* Overexpression of PD-L1 in tumor cells, however,

suppresses the proliferation, cytokine production, and cytotoxic activity of T cells. Indeed, transplantation of tumor cells expressing PD-L1 into syngeneic mice significantly increases tumor size and promotes invasion or metastasis into other organs. *Id.* That research led to the discovery that inhibiting the binding of PD-1 to its ligands, PD-L1 and PD-L2, impairs the growth of tumors via T cell activation. *Id.* Thus, many therapeutic antibodies aimed at blocking the binding of PD-1 to its ligands have been developed for the treatment of certain cancer types. *Id.*

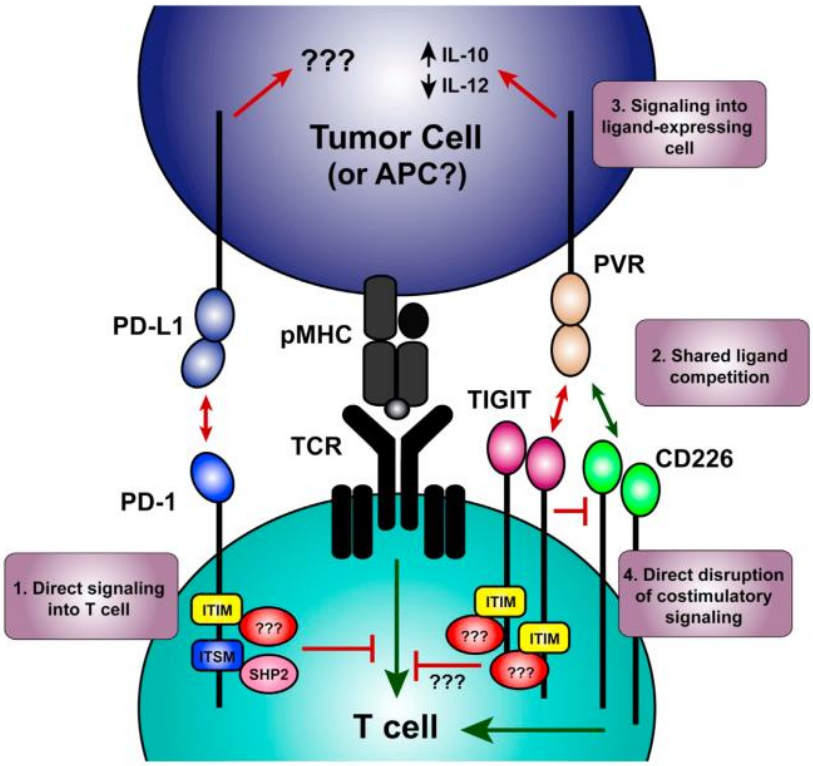
(b) TIGIT

TIGIT, an abbreviation of T-cell immunoreceptor with Ig and ITIM domains, is a transmembrane glycoprotein that belongs to a poliovirus receptor ("PVR") family of type 1 proteins. *Id.* ¶77. TIGIT is expressed by subsets of regulatory and memory CD4+ T cells, CD8+ T cells, and natural killer ("NK") cells. *Id.* In cancer, TIGIT is commonly co-expressed with PD-1 on tumor antigen-specific CD8+ T cells and CD8+ tumor-infiltrating lymphocytes (TILs) in mice and humans. *Id.*

TIGIT is an inhibitory receptor that binds two ligands, CD155 (also called PVR) and CD112. *Id.* ¶78. TIGIT competes with another receptor called CD226 for PVR binding, and while CD226 signaling enhances cytotoxicity of T lymphocytes and NK cells, TIGIT signaling exerts immunosuppressive effects. *Id.* In addition to ligand competition, it has been posited in at least one paper that TIGIT's immunomodulatory effects are due to its ability to interfere directly with

CD226 signaling by physically preventing its homodimerization. *Id.*; Ex. 1030 at 933. In experimental models, TIGIT blockade or deletion acts primarily on NK cells to augment CD8+ T cell-mediated antitumor responses and impede tumor growth. *Id.* Thus, like PD-1, therapeutic antibodies aimed at blocking TIGIT's immunomodulatory effects are being investigated for use in treating certain cancer types. Ex. 1002 ¶78.

These molecular mechanisms of the PD-1, TIGIT, and CD226 receptors are depicted in the figure below, where red lines indicate inhibitory signals and green lines indicate stimulatory signals:



Ex. 1011 at 786, Fig. 1.

VII. LEVEL OF ORDINARY SKILL IN THE ART

A POSA as of the asserted priority date of the alleged invention (or at any time point up to the filing date of the application that matured as the '836 patent) would have had a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an M.D. with similar educational background. Ex. 1002 ¶¶80-81. A POSA would also have had at least five years of experience with antibodies and antibody engineering, including the design of therapeutic antibodies. *Id.* A POSA would also have had knowledge and experience in the treatment of cancer and checkpoint inhibitors, or have had access to a person with that knowledge and experience. (*Id.*)

VIII. CLAIM CONSTRUCTION

Rules 42.104(b)(3) and (4) require a petition to identify, for each challenged claim, "[h]ow the challenged claim is to be construed" and "[h]ow the construed claim is unpatentable" under that construction. 37 C.F.R. §§ 42.104(b)(3), (4).

Claims in PGR petitions are construed using the same standard as in district court. *See* 83 Fed. Reg. 51340 (Oct. 11, 2018); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc).

A. "individual"

Each of the Challenged Claims require administration to an "individual." Moreover, each of the Challenged Claims are directed to using immune checkpoint inhibitors to treat, *inter alia*, cancer. A POSA therefore would understand that an

"individual" must both have an immune system and be susceptible to cancer. The specification explains that cancer is a "condition in mammals." Ex. 1001, 53:2. Furthermore, the specification states that an "individual" can include humans. *Id.* 5:23, 18:13-15, 27:19-20. A POSA would therefore understand that an "individual" is a "mammal, including but, not limited to, humans." Ex. 1002 ¶195 n.3.

B. "effective amount"

Independent claims 1 and 3 each require administration of an "effective amount" of two different compounds. The specification provides an explicit definition for "effective amount," Ex. 1001, 53:47-54:23, that should be used when construing this term. *Phillips*, 415 F.3d at 1316 ("[T]he inventor's lexicography governs."). As explained by the specification, an "effective amount" is "the minimum concentration required to effect a measurable improvement or prevention of a particular disorder" and "is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects." Ex. 1001, 53:47-49, 52-55. An "effective amount" "may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the antibody to elicit a desired response in the individual." *Id.* 53:49-52.

C. "cancer"

Claim 1 recites a "method of treating or delaying progression of a <u>cancer,</u>" *id.* 135:52-53, and claim 5 states "wherein the individual has a cancer." *Id.* 137:4-5.

The specification provides an explicit definition of "cancer" that should be adopted as the construction for this term. *Id.* 53:1-32; *Phillips*, 415 F.3d at 1316. According to this definition, "cancer" is "the physiological condition in mammals that is typically characterized by unregulated cell growth" and includes "benign and malignant cancers as well as dormant tumors or micrometastases" as well as each of the specific types of cancer identified in the specification. Ex. 1001, 53:1-32.

D. "a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1 and/or B7-1"

The '836 patent specification defines the term "PD-L1 binding antagonists" as "a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L1 with either one or more of its binding partners, such as PD-1, B7-1." *Id.* 39:55-59. The claims explicitly identify the required binding partners as PD-1 and/or B7-1. Thus, "a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1 and/or B7-1" means "a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L1 with PD-1 and/or B7-1.

E. "a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2"

The '836 patent specification defines the term "PD-1 binding antagonists" as "a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-1 with one or more of its binding

partners, such as PD-L1, PD-L2." *Id.* 39:29-32. As discussed above for the "PD-L1 binding antagonist," the claims explicitly identify the required binding partners as PD-L1 and/or PD-L2. Thus, "a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2" means "a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-1 with PD-L1 and/or PD-L2."

F. "a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1"

The '836 patent specification defines the term "PD-L2 binding antagonists" as "a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1." *Id.* 40:15-18. As discussed above for the "PD-L1 binding antagonist," the claims explicitly identify the required binding partner as PD-1. Thus, "a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1" means ""a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L2 with PD-1."

G. "wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody" (claim 8) and "wherein the anti-PD-L1 antibody comprises …" (claim 9)

Claim 8 depends from claims 1, 2, and 3 and states "wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody." *Id.* 137:14-15. Claim 9 depends from claim 8 and further limits "the anti-PD-L1 antibody" to one having specific

amino acid sequences. *Id.* 137:16-138:3. Based on the plain language of the claims, dependent claims 8 and 9 limit the scope of the claimed "PD-L1 binding antagonist" but do not limit the scope of the claimed "PD-1 binding antagonist" and "PD-L2 binding antagonist."

H. "an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof."

All of the Challenged Claims require "an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof." *Id.* 135:59-62, 136:53-56, 136:64-67. The specification provides a definition of "antibody" that helps inform the construction of this claim term. *Id.* 42:60-67. A POSA would thus understand that an "anti-TIGIT antibody" is an "antibody" (as that term is defined by the specification) that binds to TIGIT. And an "antigen-binding fragment thereof" refers to a portion of an antibody that retains the ability to bind to an antigen, in this case TIGIT. This is consistent both with the specification's repeated use of the term "anti-TIGIT antibody," in particular the section titled "Anti-TIGIT Antibodies," *id.* 78:17-86:26, and the naming convention used in the art of describing an antibody as "anti-[antigen]."

The term "inhibitory anti-TIGIT" is not used anywhere in the specification. In the context of this claim limitation, a POSA would understand that an "***inhibitory***

anti-TIGIT antibody" refers to the functionality recited earlier in the claim limitation, i.e., the ability to "inhibit[] and/or block[] the interaction of CD226 with TIGIT." *Id.* 135:59-60. Thus, a POSA would understand that the claimed antibody or antigen-binding fragment must have two functional properties: 1) it must bind TIGIT; and 2) it must inhibit and/or block the interaction of CD226 with TIGIT. The correct construction for this claim term therefore is "an antibody (as defined by the specification) or antigen-binding fragment that binds TIGIT and inhibits and/or blocks the interaction of CD226 with TIGIT."

IX. THE CHALLENGED CLAIMS OF THE '836 PATENT ARE INVALID

A. Ground 1: The Challenged Claims Do Not Satisfy the Written Description Requirement

To satisfy the written description requirement of Section 112(a), applicants must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification." *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (internal quotation marks omitted). "The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014). The written description requirement thus ensures "that the scope of the right to

exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field" by "curtailing claims" that the applicant has not invented and cannot describe. *Id.* at 1299 (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (*en banc*)).

"[A] sufficient description of a genus … requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (citation omitted). "Functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable [such as antibody development], where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered" by the claims. *AbbVie*, 759 F.3d at 1301; *see also Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378 (Fed. Cir. 2017).

The Challenged Claims recite the combined administration of two incredibly broad genera that are defined in purely functional terms—one directed to antibodies and antigen binding fragments that bind to TIGIT and block the interaction of TIGIT and CD226 and the other directed to binding antagonists of PD-1, PD-L1 and PD-L2. Ex. 1002 ¶¶93, 114, 121. As addressed below, neither of these functional genera are adequately described by the specification. In addition, each of the Challenged

Claims is directed to methods that include, at least, treating cancer. *Id.* ¶¶155-57. But again, the limited data in the specification failed to show that the inventors were in possession of a method to treat any and all cancers. *Id.* ¶158.

1. The Specification Does Not Adequately Describe the Genus Comprising Anti-TIGIT Antibodies Having the Claimed Functional Characteristics

All of the Challenged Claims require, *inter alia*, administering an anti-TIGIT antibody or antigen binding fragment to an "individual." The anti-TIGIT antibody is defined in purely functional terms. *Id.* ¶¶93-99. Independent claims 1 and 3 require "an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof." *Id.* ¶93; Ex. 1001, 135:59-62. Thus, for claims 1 and 3, the claimed antibody must both bind TIGIT and inhibit the interaction of CD226 with TIGIT. Ex. 1002 ¶93. Claim 7 depends from either claim 1 or 3 and contains the same functional requirements but also specifies that the anti-TIGIT antibody be "a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, or an immunotoxin." *Id.* ¶94; Ex. 1001, 137:10-13. Claims 11 and 12 recite additional functional requirements, specifically that the anti-TIGIT antibody "inhibits and/or blocks the ability of TIGIT to disrupt CD226 homodimerization," Ex. 1001, 138:15-16, or "inhibits and/or blocks the interaction of TIGIT with

CD226, without impacting PVR-CD226 interaction," respectively. *Id.*, 138:19-20; Ex. 1002 ¶95.

The claims do not limit this functionally-defined genus of anti-TIGIT antibodies to any amino acid sequence or other structural feature, nor do they specify where the antibodies must bind or whether they must have any particular binding affinity. Ex. 1002 ¶97. Rather, any antibody that binds TIGIT and meets the specified functional requirements falls within the scope of the claims. *Id.*

As an initial matter, Genentech cannot rely solely on the recited target antigen—TIGIT—to establish written description support for the functionally-claimed genus. The Federal Circuit has held that merely characterizing the protein to which an antibody binds, without more, is insufficient to establish written description support for a claimed functional genus. *Amgen*, 872 F.3d at 1378. According to the Federal Circuit, describing an antibody based on its target antigen "r[u]n[s] afoul of what is perhaps the core ruling in *Ariad*" by permitting a finding of written description support based on a showing of how a POSA could make and use an antibody to the chosen antigen target. *Id*. at 1378. It thus "flouts basic legal principles of the written description requirement" to allow "patentees to claim

antibodies by describing something that is not the invention, i.e., the antigen."[3] *Id.* Thus, antibodies are like every other type of invention and must be described either by 1) disclosing a sufficient number of representative species or 2) common structural features. *See Ariad*, 598 F.3d at 1350. The claims do not satisfy either one of these criteria.

(a) The Specification Discloses Only a Single Anti-TIGIT Antibody With the Claimed Functional Features

The functionally-defined genus of anti-TIGIT antibodies is incredibly broad. The claims cover any antibody that satisfies the recited functional features regardless of the type of antibody or its method of preparation. Ex. 1002 ¶¶97-99. Indeed, in describing "[t]he anti-TIGIT antibodies useful in this invention," Ex. 1001, 78:17, the specification goes to great lengths to emphasize the diversity of anti-TIGIT antibodies that can be used to practice the invention. The anti-TIGIT antibodies may be polyclonal or monoclonal, *id.* 78:23-24, monovalent or bivalent, *id.* 80:12, human antibodies made using either phage display or transgenic animals, *id.* 81:7-31, humanized antibodies (including chimeric antibodies), *id.* 80:26-54, bispecific

[3] In the wake of *Amgen*, the PTO issued new guidelines to examiners emphasizing that identifying an antibody by its target antigen does not satisfy the written description requirement "even when preparation of such an antibody is routine and conventional." Ex. 1031 at 1-2.

antibodies (including those that bind two different epitopes on TIGIT and those that bind TIGIT and a triggering molecule on a leukocyte or Fc receptors for IgG), *id.* 83:12-26, trispecific antibodies, *id.* at 83:8-11, heteroconjugate antibodies, *id.* 83:31-43, and antibodies having modified effector functions, *id.* 83:45-62. Moreover, a POSA would understand that multiple antibodies having different primary amino acid sequences could nonetheless bind the same epitope, i.e., have the same claimed functional properties, and that it is possible that there is more than one epitope on TIGIT that would lead to blocking or inhibiting the interaction of CD226 with TIGIT. Ex. 1002 ¶¶114-118; *see* Ex. 1020 at 227. Thus, by defining the claimed genus antibodies in purely functional terms, Genentech ensured that it would be able to cover a large and diverse genus of antibodies without any need to describe the structural features of this diverse group of antibodies.

Despite the incredible breadth of the claimed genus, Genentech provides virtually no support in the specification demonstrating that the inventors were in possession of the full scope of the functionally-defined genus. Despite running to 136 columns, the specification describes only a ***single antibody*** that meets the functional requirements of the claims. Ex. 1002 ¶101. Specifically, Examples 9 and 14 are in vitro experiments using a single "blocking" antibody, labelled clone 10A7. *Id.* ¶¶101-04, 107; Ex. 1001, 98:51-100:31; *id.* 107:40-106:59. Based on the results of these experiments, the inventors conclude that 10A7 both binds TIGIT and blocks

the interaction of CD226 with TIGIT, as required by claim 1, Ex. 1001,99:33-42; 99:58-67, and that 10A7 meets the additional functional requirements of claims 11 and 12. Ex. 1002 ¶¶105-06, 108-109. There is no data in the specification showing that any other antibody meets the claimed functional limitation of inhibiting or blocking the interaction of CD226 with TIGIT. *Id.* ¶111.

As a matter of both law and science, disclosing only a single antibody within the claimed genus cannot satisfy the written description requirement that a specification disclose a representative number species to allow a POSA to recognize or envision the genus. Legally, the Federal Circuit has explained that using broad language to describe a genus based on disclosure of a single species does not satisfy the written description requirement:

> But merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.

Ariad, 598 F.3d at 1350; *see also Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115 (2008) ("'For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot be achieved by disclosing only one species within the genus*.'" (quoting 66 Fed. Reg. 1099-01, at 1106 (emphasis in original))).

Likewise, as a matter of science, the disclosure of a single anti-TIGIT antibody that blocks the interaction between CD226 with TIGIT does not permit a POSA to recognize or visualize the other members of the genus. Ex. 1002 ¶¶114-17. To the contrary, a POSA would have no way of knowing what properties of the single disclosed species are potentially representative of the genus as a whole. *Id.* ¶118. For example, the specification does not provide any information about the epitope on TIGIT to which clone 10A7 binds, nor does it provide any other information about whether there are other epitopes on TIGIT that, if targeted by an antibody, would inhibit its interaction with CD226. Similarly, knowing only the amino acid sequence of a single antibody would not permit a POSA to know whether that amino sequence is representative of other anti-TIGIT antibodies within the clamed genus. *Id.* ¶116.

The lack of representativeness of the single disclosed species is further confirmed by the specification's broad description of the types of antibodies that "are useful for this invention," including, *inter alia*, human, humanized, bispecific, trispecific, and heteroconjugate antibodies. Ex. 1001, 80:26-54, 83:12-26, 83:31-43. In fact, dependent claim 7 explicitly recites several of these categories of antibodies. *Id.* 137:9-13; *see* Ex. 1002 ¶94. Yet, the specification does not disclose even a single example of each of these categories of antibodies. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) ("[S]imply describing a large genus

of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses."). Indeed, clone 10A7 is a hamster antibody that does not fall within any of these specified categories. Ex. 1001, 83:63-66.

Genentech may argue that the claims have additional written description based on the specification's disclosure of the amino acid sequence of a second anti-TIGIT antibody, clone 1F4. However, the specification provides no data whatsoever that clone 1F4 meets the functional requirement of blocking or inhibiting the interaction of CD226 with TIGIT.[4] To the contrary, the prior art states that clones 1F4 and 10A7 bind to different epitopes on TIGIT such that both clones can simultaneously bind TIGIT. Ex. 1045 at [0145]; *see* Ex. 1002 ¶111. Given these different epitopes, without data demonstrating that clone 1F4 blocks or inhibits the

[4] The only experimental data relating to clone 1F4 is a TR-FRET analysis using cells that endogenously express TIGIT and CD226. Ex. 1002 ¶110. In that experiment, a donor fluorophore was conjugated to 1F4 and a receptor fluorophore was conjugated to an anti-CD226 antibody. *Id.* The two antibodies came in close enough contact to generate a strong FRET signal. Ex. 1001, 108:37-51,109:34-110:21 This data does not show blocking of the interaction between CD226 and TIGIT. Ex. 1002 ¶111.

interaction of CD226 with TIGIT, a POSA would have no way of knowing whether it meets the claimed functional limitations for the anti-TIGIT antibody.

(b) The Specification Does Not Disclose any Common Structural Features for Anti-TIGIT Antibodies

Because the specification does not describe a sufficient number of representative species, the only other way for Genentech to satisfy the written description requirement is to describe common structural features that would allow a POSA to recognize or visualize the full scope of the claimed genus. As an initial matter, courts have repeatedly recognized that because of the lack of a known structure/function correlation between antibody structure and the claimed functions, claims directed to broad genera of antibodies are "inherently vulnerable" to written description challenges. *AbbVie*, 759 F.3d at 1301; *see also Morphosys AG v. Janssen Biotech, Inc.*, 358 F.Supp.3d 354, 367 (D. Del. 2019) ("Given the undisputed lack of a known relationship between an antibody's structure (its sequence) and its function (its binding properties), the only reasonable conclusion is that the specification does not sufficiently disclose structural features common to the members of the genus."). That is the case here.

As in these previous cases, there is no relationship between the claimed functional properties—binding TIGIT and blocking the interaction between CD226 and TIGIT—and the structural characteristics of antibodies having that function. Ex. 1002 ¶113. The specification does not contain any information about the structural-

functional relationships for anti-TIGIT antibodies having the claimed functional properties, and having only a single example of an anti-TIGIT antibody having the claimed functional properties makes it impossible to identify any common structural features. *Id.* ¶114. Indeed, it is well known in the literature that it is highly unpredictable to identify an antibody's binding properties (e.g., affinity and activity) based on its amino acid sequence. *Id.* ¶115; Ex. 1020 at 227.

Due to this missing correlation, if one of skill generates a new antibody sequence, she simply cannot know—and the patents do not tell her—whether it falls within the claims. The only way to identify species of the claimed genera is to undertake a massive screening program. *Id.* ¶¶116-17, 209-10. Requiring "trial-and-error research" to "distinguish infringing [antibodies] from non-infringing" antibodies does not satisfy the written description requirement. *See Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 919, 926 (Fed. Cir. 2004).

* * *

In sum, the specification discloses only a single species within the genus of anti-TIGIT antibodies that block the interaction of CD226 with TIGIT. This single species cannot as a matter of law or science constitute a sufficient number of representative species to allow a POSA to recognize or visualize the full scope of the genus. Drawing a fence around a perceived genus, while leaving it to others to

implement a research program to explore the unknown contours of the genus, is simply not sufficient. *See AbbVie*, 759 F.3d at 1300 (citing *Ariad*, 598 F.3d at 1353).

2. The Specification Does Not Adequately Describe the Genus Comprising Binding Antagonists of PD-1, PD-L1 And PD-L2

Independent claims 1 and 3 also separately require, *inter alia*, administering a genus of "binding antagonists" made up of three separate subgenera: "a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1 and/or B7-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1." Ex. 1001, 136:53-58, 137:59-64. These three categories of binding antagonists are collectively referred to herein, as "PD-1 axis binding antagonists." Claims 8 and 9 limit one of the three claimed subgenera—the PD-L1 binding antagonist—to an antibody (claim 8) and a specific antibody sequence (claim 9), but these claims do not limit the other two claimed subgenera. *Id.* 137:14-138:3.

The claimed genus of PD-1 axis binding antagonists is defined in purely functional terms based on the ability to inhibit the binding of a receptor to its ligand. Ex. 1002 ¶120. The claims do not limit the recited PD-1 axis binding antagonists to any particular structural feature. *Id.* In fact, the claims do not even limit the recited genus of PD-1 axis binding antagonists to any particular type of antagonist. *Id.* ¶121-22. Rather, according to the broad definition in the specification, the claimed antagonists can include "antibodies, antigen binding fragments thereof,

immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of [PD-1/PD-L1/PD-L2] with one or more of its binding partners." Ex. 1001., 39:36-42, 39:62-40:2, 40:22-28. Thus, any antagonist that inhibits the binding of PD-1, PD-L1, or PD-L2 to their particular binding partner(s) falls within the broad scope of the claims. Ex. 1002 ¶123.

As established above, to satisfy the written description requirement for this claimed functional genus of PD-1 axis binding antagonists, the specification must permit a POSA to visualize or recognize the members of the genus by disclosing either: (1) a sufficient number of representative species or (2) structural features common to the members of the genus. *See Ariad*, 598 F.3d at 1350. The specification does neither. The Challenged Claims are therefore invalid for failing to satisfy the written description requirement with respect to the claimed PD-1 axis binding antagonists.

(a) The Specification Fails to Disclose a Sufficient Number of Representative Binding Antagonists of PD-1, PD-L1 and PD-L2

The claimed genus of PD-1 axis binding antagonists is even broader than the claimed genus of anti-TIGIT antibodies in two significant ways. First, the claimed binding antagonists are not limited to antibodies but also encompass a wide array of disparate molecules such as antibodies, antigen binding fragments thereof,

immunoadhesins, fusion proteins, oligopeptides, small-molecule inhibitors, and more. Ex. 1001, 39:36-42, 39:62-40:2, 40:22-28; *see* Ex. 1002 ¶121. Indeed, the specification emphasizes that "[t]he term 'antagonist' is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native polypeptide disclosed herein." Ex. 1001, 40:45-48. Second, the claimed binding antagonists consists of three very broad subgenera—PD-1 binding antagonists, PD-L1 binding antagonists, and PD-L2 binding antagonists—each of which must be adequately described. *See Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367-68 (2011) (finding patent invalid for lack of written description where specification failed to adequately describe subgenus of claimed genus); *Fujikawa*, 93 F.3d at 1571 (Fed. Cir. 1996) ("[S]imply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses.").

Despite the breadth of the claimed genus of PD-1 axis binding antagonists, the specification contains scant disclosure of species within that genus. Ex. 1002 ¶125. The specification specifically names only three anti-PD-1 antibodies called MDX-1106 (nivolumab), Merck 3745 (lambrolizumab), and CT-011 (pidilizumab)); four anti-PD-L1 antibodies called 25A1 (suitable only for use in mice), MDX-1105,

MEDI 4736, and MPDL3280A[5]; and one immunoadhesin called AMP-224. *See, e.g.*, Ex. 1001, 7:20-25, 50:4-6, 63:60-67, 64:12-15, 101:53-58; Ex. 1002 ¶¶125-26. Thus, across the entire claimed genus of PD-1 axis binding antagonists, the specification discloses only eight examples—seven antibodies and one immunoadhesin. Notably, only one of these antagonists, 25A1, was used in the examples of the '836 patent. *Id.* ¶128; Ex. 1001 at 101:53-63.

The eight disclosed species are not representative of the full scope of the genus of PD-1 axis binding antagonists. Ex. 1002 ¶129-130. First, there is no disclosure of any PD-1 axis binding antagonist other than an antibody or an immunoadhesin. *Id.* ¶131. The claimed genus of PD-1 axis binding antagonists, however, is much broader than antibodies and immunoadhesins. It includes, for example, small molecules, oligopeptides, and fusion proteins other than immunoadhesins. The '836 patent, however, fails to describe even a single species for these categories of

[5] The '836 patent also discusses slight sequence modifications to the variable region of MPDL3280A, including an antibody called YW243.55.S70. *See, e.g.*, Ex. 1001, 63:62-65; Ex. 1002 ¶129. Even if these slightly modified sequences are included in the number of anti-PD-L1 antibodies disclosed by the '836 patent, it does not change the fact that the '836 patent describes a very small and narrow subset of species compared to the large and diverse genus it claims. Ex. 1002 ¶129.

antagonists. This complete failure to disclose any species for many of the categories of claimed PD-1 axis binding antagonists is alone sufficient to show lack of written description. *See Boston Scientific*, 647 F.3d at 1367-68; *Fujikawa*, 93 F.3d at 1571.

Second, there is no disclosure of any antagonist that targets PD-L2. Ex. 1002 ¶135. The specification is clear, for example, that anti-PD-L2 antibodies are one type of claimed PD-L2 binding antagonist. Ex. 100, 40:22-23. Yet the specification fails to describe even one example of an anti-PD-L2 antibody, much less any molecule that binds to PD-L2. This failure is yet another independent reason the ’836 patent lacks written description over the claimed genus of PD-1 axis binding antagonists. *See Boston Scientific*, 647 F.3d at 1367-68; *Fujikawa*, 93 F.3d at 1570.

Third, the sole immunoadhesin disclosed in the ’836 patent—AMP-224—is not representative of all immunoadhesins covered by the claims. Ex. 1002 ¶136. AMP-224 only binds to PD-1, *id.*; Ex. 1001 63:65-66, 64:12-15; Ex. 1033 at Abstract; Ex. 1034 at 3, and there is no disclosure in the ’836 patent of any immunoadhesin that binds to PD-L1 or PD-L2. But even within the category of immunoadhesins that bind to PD-1, a single species such as AMP-224 cannot represent this entire category. *See, e.g.*, *Ariad*, 598 F.3d at 1350; *Carnegie Mellon*, 541 F.3d at 1124.

Finally, the specification’s limited disclosure of three anti-PD-1 antibodies and four anti-PD-L1 antibodies is not representative of the full scope of anti-PD-1

or PD-L1 antibodies covered by the claims. Ex. 1002 ¶137. As an initial matter, anti-PD-L1 antibody 25A1 is an anti-mouse PD-L1 antibody that cannot be representative of anti-human PD-L1 antibodies. Ex. 1002 ¶138. Moreover, there are no common structural features across the remaining six disclosed antibodies that would allow a POSA to visualize or recognize the other antibodies that would fall within the scope of the claims. In fact, the three disclosed anti-PD-1 antibodies share as little as 53.1% sequence homology for the heavy chain variable regions and as little as 66.98% sequence homology for the light chain variable regions. Ex. 1002 ¶139; Ex. 1003 ¶¶9-13. Similarly, the three disclosed anti-human-PD-L1 antibodies share as little as 50% sequence homology for the heavy chain variable regions and as little as 71.03% sequence homology for the light chain variable regions. Ex. 1002 ¶140; Ex. 1003 ¶¶19-23. In fact, some of the disclosed antibodies share more sequence homology in their heavy and/or light chain variable regions with antibodies that bind different targets than they do with one another. Ex. 1002 ¶¶139-40; Ex. 1003 ¶¶15-18, 25-28. Given their distinct amino acid sequences, many of the antibodies disclosed in the ’836 patent have been shown to bind to their respective targets with different binding affinities and at different epitopes. Ex. 1002 ¶137; Ex. 1035 at 137-138; Ex. 1036 at 2, 4-5. The ’836 patent, however, provides no disclosure about the epitopes that the PD-1 axis binding antagonists should bind. Ex. 1002 ¶142, 152.

The significant divergence of the small number of anti-PD-1 and anti-PD-L1 antibodies disclosed in the ’836 patent makes it impossible for a POSA to assess what characteristics of those antibodies should be considered representative of the genus as a whole. Ex. 1002 ¶143. A POSA therefore would not be able to rely on the patent’s limited disclosures to visualize or recognize the many other antibodies that fall within the scope of the genus of PD-1 axis binding antagonists covered by the claimed methods, much less the other non-antibody binding antagonists that are encompassed by the claims. *Id.*

Indeed, many anti-PD-1 and anti-PD-L1 antibodies are now known that were not described in the ’836 patent and that are highly divergent from the few antibodies that are described. *Id.* ¶144. For example, two antibodies—cemiplimab-rwlc (anti-PD-1 antibody) and avelumab (anti-PD-L1 antibody)—have been FDA-approved for use in treating certain cancers and do not share significant sequence similarity to the ’836 patent’s disclosed antibodies. Ex. 1037; Ex. 1038; Ex. 1002 ¶144; Ex. 1003 ¶¶17-18, 27-28, Table 7, 8, 15, 16.

In addition to the antibodies that have been FDA-approved, many other PD-1 axis binding antagonists have been identified in the literature and/or are under development for clinical use that bear little resemblance to anything disclosed in the ’836 patent—including not only antibodies but oligopeptides and small molecules. Ex. 1002 ¶¶145-149; Ex. 1003 ¶¶15-18, 25-28. This large variety of

diverse antagonists confirms that the genus of PD-1 axis binding antagonists covered by the claimed methods cannot be represented by the seven antibodies and one immunoadhesin disclosed in the ’836 patent. See Ex. 1002 ¶149.

(b) The Specification Does Not Disclose any Common Structural Features for Binding Antagonists of PD-1, PD-L1 and PD-L2

In addition to failing to disclose a representative number of species, the ’836 patent also fails to disclose any common structural features that would allow a POSA to visualize or recognize the members of the claimed genus of PD-1 axis binding antagonists. Ex. 1002 ¶151. The patent, in fact, does not describe any structural features of PD-1 axis binding antagonists at all beyond disclosing the seven antibodies and one immunoadhesin discussed in the preceding section.

As an initial matter, the structure of the disclosed antibodies and immunoadhesin would not tell a POSA anything about other categories of antagonists such as oligopeptides, fusion proteins other than immunoadhesins, and small molecules that are encompassed within the claimed genus. *Id.* ¶152. But even with respect to antibodies and immunoadhesins, it is well accepted that there is no predictable relationship between the structure of these molecules and their function. *Id*. ¶146; *AbbVie*, 759 F.3d at 1301; *Morphosys*, 358 F. Supp. 3d at 367. Immunoadhesins are also unpredictable. Ex. 1002 ¶154. This unpredictability is confirmed by the existence of many known PD-1 axis binding antagonists that

successfully inhibit the PD-1 pathway but do not share many, if any, common features with one another. *Id.* ¶153.

Indeed, there is only one way to determine whether a newly generated antibody or immunoadhesin will possess particular functional properties. The skilled artisan must test it. *Id.* ¶154. As described above with respect to anti-TIGIT antibodies, such a "trial-and-error" research plan cannot satisfy the written description requirement. *See Univ. of Rochester*, 358 F.3d at 926.

* * *

In sum, the '836 patent specification discloses only eight species within the broad genus of PD-1 axis binding antagonists. These disclosed species and the other vague functional disclosures of the '836 patent do not permit a POSA to recognize or visualize the full scope of the genus. Not only do the disclosed species wholly exclude subgenera of the broad genus of PD-1 axis binding antagonists—such as small molecules, oligonucleotides, fusion proteins other than immunoadhesins, and anti-PD-L2 antibodies—but they are also insufficient to represent the large and unpredictable subgenera of anti-PD-1 and anti-PD-L1 antibodies and immunoadhesins to which they belong. Moreover, only one of the disclosed species was used in the examples in the patent. For all these reasons, Genentech's claim to all PD-1 binding antagonists that achieve a particular functional result therefore is not adequately described.

3. The Specification Does Not Adequately Describe the Genus Of Treating Any And All Types of Cancer

All of the Challenged Claims cover methods to treat "cancer." Ex. 1001, 135:52-53. Claim 1 does explicitly; claim 3 is more generally directed to stimulating an immune response, but claim 5 depends from claim 3 and adds the limitation "wherein the individual has cancer." *Id.* 136:57-58, 137:4-5. Claim 10 in turn depends from claims 1 or 5 and identifies 25 specific types of cancer that are being treated. *Id.* 138:4-12. Thus, based solely on the claim language, all of the Challenged Claims ***at a minimum*** cover treating 25 types of cancer. Ex. 1002 ¶156. The specification defines the generic term "cancer" even more broadly. *Id.* 53:1-32.

A POSA would understand that "cancer" is an extremely broad concept and that different cancers have different etiologies and mechanisms of development, respond differently to cancer therapies, and require different treatment approaches. Ex. 1002 ¶157. In particular, a POSA would understand that different types of cancer respond to immune checkpoint inhibitors differently. *Id.* These are some of the reasons that treating cancer is highly unpredictable. *Id.* Given this understanding, data showing that a particular checkpoint inhibitor, or in this case combination of checkpoint inhibitors, can be used to treat one type of cancer does not support the conclusion that these same checkpoint inhibitors could be used to treat other types of cancer. *Id.* ¶158.

Despite claiming methods that can be used to treat any type of cancer, including the 25 specific types of cancer listed in claim 10, the specification fails to provide a correspondingly broad disclosure to demonstrate that the inventors were in possession of the full scope of the claimed invention. The specification provides data for only three murine cancer strains: CT26 colorectal cancer, MC38 colon carcinoma, and EMT6 breast carcinoma. *Id.* ¶159; Ex. 1001, 95:15-96:53. A POSA would understand that a colon carcinoma is a type of colorectal cancer; therefore, the specification provides data for only two types of cancer. Ex. 1002 ¶159. Given the diverse properties of different cancers, three specific strains—and only two types—of cancer are not representative of all cancers. *Id.* ¶160. Based on the limited data in the patent, especially in light of the highly unpredictable nature of cancer treatment, a POSA would not conclude that the inventors were in possession of a method that can could be used to treat ***any*** type of cancer, including each of one the 25 types of cancer specified in claim 10. *Id.* ¶161; *see Charleston Med. Therapeutics, Inc. v. AstraZeneca Pharm. LP*, No. 2:13-CV-2078-RMG, 2016 WL 7030743, at *12 (D.S.C. Feb. 19, 2016) ("Plaintiffs have attempted to obtain a lottery ticket in return for a hypothesis; if it turns out that any one (or combination) of these nine categories of compounds is effective in treating any one of 90+ diseases, Plaintiffs win the lottery. This is not the purpose of patent protection").

Genentech may try to rely on broad statements in the specification that the claimed methods can be used to treat any type of cancer, but absent additional specific support in the specification these generalized statement are legally insufficient to provide written description support. "[G]eneric claim language appearing *in ipsis verbis* in the original specification does not satisfy the written description requirement if it fails to support the scope of the genus claimed." *Ariad*, 598 F.3d at 1350. Rather, Genentech did exactly what the Federal Circuit forbade in *Ariad*—it "merely recite[d] a description of the problem to be solved while claiming all solutions to it and, … cover[ing] any compound later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention." *Id.* at 1353. Because the inventors were not possession of a method to treat all types of cancer, the Challenged Claims lack written description.

B. Ground 2: The Challenged Claims Are Not Enabled

"Enablement is a question of law based on underlying factual findings." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). "Enablement serves the dual function in the patent system of ensuring adequate disclosure of the claimed invention and of preventing claims broader than the disclosed invention." *Id*. at 1380-81.

To be enabling, "a patent must teach those skilled in the art how to make and use the ***full scope*** of the claimed invention without 'undue experimentation.'" *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). "Thus, a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." *MagSil*, 687 F.3d at 1381. "The scope of the claims must be less than or equal to the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Id*. (internal quotation marks omitted). Although "a specification need not disclose what is well known in the art," "[t]ossing out the mere germ of an idea does not constitute enabling disclosure…. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech*, 108 F.3d at 1366. "[A]n iterative, trial-and-error process" necessary to practice the full scope of the claims may establish undue experimentation to support a finding of non-enablement. *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010); *see also Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013) (holding that "having to synthesize and screen each of at least tens of thousands of candidate compounds constitutes undue experimentation").

Here, practicing the full scope of the claims requires undue experimentation in at least four ways: (1) making and screening the full scope of the genus of claimed

anti-TIGIT antibodies; (2) making and screening the full scope of the genus of claimed PD-1, PD-L1 and/or PD-L2 binding antagonists; (3) determining the "effective amount" of anti-TIGIT antibodies and PD-1, PD-L1 and/or PD-L2 binding antagonists for all combinations of these two genera and for all "individuals" and (4) using the recited compounds to treat any and all types of cancer. Any of these categories is alone sufficient to establish the invalidity of the Challenged Claims for lack of enablement, but taken together, they collectively illuminate the complete disconnect between the scope of the claimed subject matter and the teachings in the specification.

Undue experimentation factors include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

1. The Nature of the Invention and the Breadth of the Claims

The invention is drawn to a method of stimulating an immune response in an animal by co-administering a large genus of PD-l, PL-L1, or PD-L2 binding antagonists and a second large genus of anti-TIGIT antibodies that block TIGIT's interaction with CD226. Ex. 1002 ¶163. The specification identifies cancer

treatment as a particular application for this heightened immune response and the specification identifies humans as one type of "individual" that can be treated with the invention. *Id.*

The Challenged Claims similarly are extremely broad. *Id.* ¶164. The two challenged independent claims—claims 1 and 3—are directed to "[a] method of treating or delaying progression of a cancer in an individual," Ex. 1001, 135:52-53, and "[a] method of increasing, enhancing, or stimulating an immune response or function in an individual," respectively. *Id*. 136:57-59. As evidenced by dependent claim 5, the method of claim 3 covers treating individuals with cancer and is thus at least as broad as claim 1. *Id.* 137:4-5. Both claims 1 and 3, are directed to treating any "individual" with an "effective amount" of two extremely broad categories of molecules: (1) PD-l, PL-L1, or PD-L2 binding antagonists; and (2) inhibitory anti-TIGIT antibodies or antibody fragments. *Id.* 135:52-62; *id.* 136:57-67; Ex. 1002 ¶165. Claim 6 limits the methods to cancers having elevated levels of T cell infiltration, while claim 10 identifies 25 types of cancers that can be treated with the claimed method. Ex. 1001, 137:6-7, 138:4-13. Each of these dependent claims cover an incredibly broad group of cancers but also highlight that claims 1 and 3, are even broader because they cover treating and all types of cancer. Ex. 1002 ¶166.

As discussed above in Section IX.A, *supra*, the claimed genus of functionally-defined inhibitory anti-TIGIT antibodies encompasses a large and diverse group of

compounds. Claims 7, 11, and 12 each narrow the scope of the genus of anti-TIGIT antibodies, but in each case the genus is still functionally defined with an unknown scope. *Id.* ¶166. None of the Challenged Claims recite a specific anti-TIGIT antibody or antibody fragment to be used. *Id.* ¶¶93-99, 165-70.

Likewise, as described in Section IX.A.2, *supra*, the claimed genus of PD-l, PL-L1, and/or PD-L2 binding antagonists also is extremely broad and diverse. The claimed PD-l, PL-L1, and PD-L2 binding antagonists are not limited to antibodies; they include any type of compound that blocks or inhibits PD-l, PD-L1, or PD-L2's interaction with their binding partners. *Id.* ¶¶118-122; Ex. 1001, 39:36-42, 39:62-40:2, 40:22-28, 40:45-48. Claims 8 and 9 limit the PD-L1 binding antagonist to PD-L1 antibodies (claim 8) and an antibody having a specific CDR sequences (claim 9). Ex. 1002 ¶168. However, neither of these claims limits the PD-1 or PD-L2 binding antagonist; therefore, the scope of claim 8 and 9 is still incredibly broad. *Id.*

2. The Level of Ordinary Skill in the Art

The level of ordinary skill in the art is high: an ordinary skilled artisan needs specialized knowledge of cancer and immunology. Ex. 1002 ¶170.

Developing and testing a cancer therapeutic or a therapeutic for stimulating an immune response is difficult, complicated, and highly unpredictable because there are many different cancers, each with different etiologies, development, and treatment. *Id.* ¶168, 171. Similarly, generating antibodies having a specified

therapeutic effect requires a high level of skill. *Id.* ¶172. Likewise, generating PD-1, PD-L1 and PD-L2 binding antagonists, including non-antibody binding antagonists, requires a high degree of skill. *Id.* ¶173.

3. State of the Art and Level of Predictability

Cancer therapy is a highly unpredictable art. *Id.* ¶¶202-08. There are many different types of cancer. They each develop in different ways, and each type can require different treatment approaches. This is evidenced by the vast array of potential therapies—radiation, surgery, chemotherapeutics, and targeted therapeutics—and the use of multiple therapies to treat some cancers. This is also evidenced by the varying degrees to which targeted cancer therapeutics work across different cancer types. Ex. 1002 ¶201, 205-07; *see* Ex. 1039 at 4.

The specific field of cancer immunotherapy also is particularly unpredictable due at least in part to the limitations of pre-clinical animal studies. Indeed, a number of cancer-specific immunotherapeutics that were successful in animal models have produced mixed results in human clinical trials. Ex. 1002 ¶¶203-05; Ex. 1040 at 115; Ex. 1042 at 2.

Moreover, generating antibodies for therapeutic use is highly unpredictable. There is no known correlation between an antibody's amino acid sequence and its binding properties, and it is known that antibodies having similar binding properties can have vastly different structural characteristics. *See, e.g.*, Ex. 1002 ¶115.

Similarly, generating non-antibody binding antagonists for therapeutic use is also highly unpredictable. The ’836 patent teaches that binding antagonists are any “molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction” of PD-1, PD-L1 or PD-L2 with their binding partners. Ex. 1001, 39:29-32, 39:55-58, 40:15-18. In addition to antibodies, this broad class of compounds includes small molecules, immunoadhesins, fusion proteins, and oligopeptides, each of which are highly unpredictable for therapeutic use as a PD-1, PD-L1 or PD-L2 binding antagonist. Ex. 1002 ¶132-137. Indeed, the immunoadhesin identified by the patent as a PD-1 binding antagonist, AMP-224, was subsequently abandoned after showing little to no efficacy in pilot studies in colorectal cancer patients despite anti-PD-1 antibodies showing efficacy in patients with the same type of cancer. *Id.* ¶128, 137; Ex. 1034 at 3; Ex. 1033 at Abstract; Ex. 1041 at 2-3.

4. The Absence of Working Examples

The working examples in the ’836 patent provide virtually no guidance for practicing the full scope of the claimed invention. The data in the patent is limited to in vitro assays, as well as a few experimental studies in mice. Ex. 1002 ¶177-92. The in vitro assays do not assess the therapeutic effectiveness of administering a combination of an anti-TIGIT antibody with the claimed functional properties and a PD-1, PD-L1, and/or PD-L2 binding antagonist. *Id.* ¶¶192. The mouse studies

assess therapeutic effectiveness in only two types of cancer—the well-known test platforms, CT26 and MC38, both of which are colorectal cancers, and EMT6, a breast cancer—and a single viral strain—another well-known test platform, LCMV. *Id.* ¶¶178,191; Ex. 1001, 93:32-94:31; *id.* 95:10-97:28; *id.* 101:33-101:19; *id.* 106:43-107:38. And the mouse studies described in the examples use only a single anti-TIGIT antibody, clone 10A7, in combination with a single anti-PD-L1 antibody, clone 25A1. Ex. 1002 ¶¶187-88.

The ’836 patent does not provide any working examples using the claimed methods in humans, human cells, or in any type of cancer other than colorectal and breast cancer. *Id.* ¶¶190-91. It also does not provide any working examples using any other PD-1, PD-L1 or PD-L2 binding antagonists or any other anti-TIGIT antibody aside from the one anti-TIGIT and one anti-PD-L1 antibody used in the working examples. *Id.*

5. The Absence of Guidance in the Specification

The ’836 patent sets forth a very broad hypothesis that is repeated in the claims: that ***any*** PD-1, PD-L1, or PD-L2 binding antagonist can be used in combination with ***any*** anti-TIGIT antibody that blocks the interaction between CD226 and TIGIT in ***any*** individual to either stimulate an immune response or treat ***any*** form of cancer. *See id.* ¶191. Yet, the specification provides very little guidance to support the breadth of the claims.

First, the specification provides no guidance on how to make and screen the claimed anti-TIGIT antibodies or the claimed PD-1, PD-L1, and PD-L2 binding antagonists. *Id.* ¶¶193-194. The patent does not provide any techniques to test whether a particular antibody or binding antagonist meets the claimed functional limitations. *Id.* Nor does the patent provide any guidance about what modifications, if any, could be made to the two disclosed anti-TIGIT antibodies or all of the disclosed anti-PD-1 or PD-L1 antibodies to obtain antibodies within the scope of the claims. *Id.* ¶194. Similarly, the specification provides virtually no guidance about how make non-antibody PD-1 axis binding antagonists within the scope of the claims. *Id.*

Second, the specification provide no guidance on how to identify which "individuals" can be treated using the claimed methods. A POSA would understand that an "individual" includes humans. *See* Section VIII.A, *supra*; Ex. 1002 ¶195. Moreover, the specification does not provide any guidance regarding which individuals within a given species may be effectively treated using the claimed methods. Ex. 1002 ¶196. Nor does the specification provide any guidance about how to select a particular PD-1, PD-L1, or PD-L2 binding antagonist or particular anti-TIGIT antibody for use in a given individual. *Id.* Thus, in order to enable the full scope of the Challenged Claims, a POSA would need to run numerous tests on

each of the possible combinations of the two genera of compounds. Ex. 1002 ¶¶209-227.

Third, the specification provides virtually no guidance regarding the "effective amount" of a PD-1, PD-L1, or PD-L2 binding antagonist or an anti-TIGIT antibody. *Id.* Example 5 states that "200 μg anti-PD-L1, 500 μg anti-TIGIT, or 200 μg anti-PD-L1+500 μg anti-TIGIT antibodies" were administered to mice "for three weeks," Ex. 1001, 95:43-46, but the specification does not state how often these amounts were administered. Ex. 1002 ¶199. Otherwise, the specification provides no information whatsoever about the proper dosage, dosing regimen, route of administration, or duration of administration necessary to achieve the claimed immune response or treatment of cancer in, for example, a human. *Id.* ¶200. In particular, there is no guidance in the specification about determining an "effective amount" for antagonists other than the two used in the working examples. *Id.* ¶201 Nor is there any guidance about determining an "effective amount" in humans based on the limited murine data found in the working examples or how the "effective amount" will vary across different species or different individuals within a particular species, e.g., based on type of cancer, age or sex. Ex. 1002 ¶200. This is particularly problematic given that it was known as of the priority date that the safety and efficacy of therapeutic antibodies in preclinical animal models did not necessarily translate to human clinical trials. *See* Ex. 1040 at 115.

Finally, the specification provides no guidance about which cancers can be treated with a particular combination of PD-1, PD-L1, or PD-L2 binding antagonist and an anti-TIGIT antibody. Ex. 1002 ¶195. As noted above, the only working examples in the specification involve murine cancer models that are used with one anti-TIGIT antibody and one anti-PD-L1 antibody. Ex. 1002 ¶201. The specification provides no teaching about how this limited data can be applied across all cancers in any individual using any anti-TIGIT antibody and any anti-PD-L1 antibody. *See* Ex. 1002 ¶195.

6. Practicing the Full Scope of the Claims Requires Undue Experimentation

To practice the full scope of the Challenged Claims, a POSA would need to engage in extensive, and undue experimentation.

First, a POSA would need to make new anti-TIGIT antibodies by inoculating an animal or screening known antibody libraries for anti-TIGIT antibodies using phage. *Id.* ¶¶209-10. Once these new antibodies were generated, they would need to be tested to see if they meet the claimed functional properties. *Id.* ¶¶210-11. This includes the functional properties recited by independent claims 1 and 3 as well as the additional functional properties recited in claims 11 and 12. However, because the patent does not disclose any assay for assessing whether an antibody meets the claimed functional properties, a POSA would first have to design one. *Id.* This task is particularly difficult given that the claims require that the claimed functionality be

achieved in "an individual." Any assay or other test for assessing an antibody's functionality would need to take this into account.

Once a proper test methodology for assessing the functional limitations was designed (assuming that is possible) each new antibody would need to be iteratively tested to see if it meets the claimed functional limitations for the anti-TIGIT antibody. *Id.* ¶¶208-226. Even if this repetitive trial and error process for identifying the claimed anti-TIGIT antibodies was the only experimentation required to practice the claims, it would be undue experimentation. *Wyeth*, 720 F.3d at 1385-86 (holding that "having to synthesize and screen each of at least tens of thousands of candidate compounds constitutes undue experimentation").

But identifying the full scope of the claimed anti-TIGIT antibody is only the beginning of the experimentation necessary to practice the full scope of the Challenged Claims. Next, a POSA would need to perform a similar task for the claimed PD-1, PD-L1 and PD-L2 binding antagonists. As an initial matter, anti-PD-1, anti-PD-L1 and anti-PD-L2 antibodies are explicitly within the scope of the claimed binding antagonists. *Id.* ¶¶212-213. Thus, a POSA would need to follow a research program similar to the one described above with respect to anti-TIGIT antibodies to identify the full scope of anti-PD-1, anti-PD-L1 and anti-PD-L2 antibodies that meeting the functional requirement of the claimed binding antagonists.

However, because the claimed binding antagonists are not limited to antibodies, a POSA would need to perform even more experimentation to examine all types of molecules necessary to practice the full scope of the claims. *Id.* ¶213. A POSA would first need to determine how to make each of an extremely broad category of potential non-antibody binding antagonists. *Id.* Given the lack of guidance in the specification, a POSA would need to conduct significant experimentation to design any of these non-antibody binding antagonists. For example, to make fusion proteins—one example of a non-antibody binding antagonist identified in the specification—a POSA would need to identify which domain(s) of PD-1, PD-L1 or PD-L2 should be included in the fusion protein and then select a domain from a different protein to include in the fusion protein, express the fusion protein, harvest the fusion protein, and then test it to see if it had the claimed functionality. *Id.* ¶¶213-14. This same iterative process would need to be followed for all other types of non-antibody binding antagonists within the scope of the claims. Again, this repeated trial and error process—both for the claimed binding antagonists that are antibodies and the ones that are not—is alone sufficient to establish that undue experimentation is required to practice the claimed invention.

But even after making and identifying the full scope of the claimed anti-TIGIT antibodies and the claimed PD-1, PD-L1 and PD-L2 binding antagonists, a POSA would need to conduct even more experimentation to practice the full scope of the

claims. First, a particular anti-TIGIT antibody and a particular PD-1, PD-L1 or PD-L2 binding antagonist would need to be selected and tested for compatibility with one another. *Id.* ¶216. This compatibility would need to be tested in the context of the specific "individual" that is being treated. *Id.*

Second, once a particular anti-TIGIT antibody and a particular PD-1, PD-L1 or PD-L2 binding antagonist is selected, the "effective amount" of each one of these would need to be determined. *Id.* ¶217. The specification makes clear that determining the "effective amount" requires consideration of a number of factors and is dependent upon the individual being treated and the particular antibody:

> An "effective amount" is at least the minimum concentration required to effect a measurable improvement or prevention of a particular disorder. ***An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the antibody to elicit a desired response in the individual***. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects…. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such

> as via targeting, delaying the progression of the disease, and/or prolonging survival…. An effective amount can be administered in one or more administrations.

Ex. 1001, 53:47-54:10. This multifactorial analysis for determining an "effective amount" requires extensive experimentation, including evaluation of the dose, dosing regimen, length of treatment, and route of administration, among others. In addition, as noted in the specification the characteristics of the individual being treated may also impact the "effective amount." These factors can be fully assessed only through iterative testing where each factor affecting the "effective amount" is studied. *See* Ex. 1002 ¶¶217-219.

Moreover, if the individual being treated is a human, as is clearly contemplated by the specification, *see, e.g.*, Ex. 1001, 3:50-54, determining the "effective amount" would require extensive experimentation, including potentially human clinical trials, to assess whether "any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects." *Id.* 53:52-55. Repeating this analysis for each pair of anti-TIGIT antibody and PD-1, PD-L1 or PD-L2 binding antagonist would require staggering amounts of experimentation. Ex. 1002 ¶219.

Finally, even after the "effective amount" was determined, a POSA would still need to conduct experiments regarding which cancers can be effectively treated using the claimed methods. Ex. 1002 ¶¶220-23. Aside from identifying the twenty-

five cancers listed in claim 10, the specification does not provide any guidance on this point. Yet, even within a particular type of cancer, it is known that immune checkpoint inhibitors are effective in only some situations that depend on the specific characteristics of the cancer. *Id.* ¶205; Ex. 1042 at 2. Thus, without any additional guidance, a POSA would be forced to experiment to determine which cancers can be effectively treated using the claimed methods.

* * *

In short, the specification of the '836 patent "provides only a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. Based on the analysis of the *Wands* factors set forth above, and given the broad scope of the claims, the lack of guidance provided in the specification, and the highly unpredictable nature of not only generating and screening antibodies and other antagonists but also treating individuals with a range of possible therapeutic combinations across a range of cancers, a POSA would have to engage in undue extensive experimentation to even attempt to practice the full scope of the Challenged Claims. Therefore, the Challenged Claims are invalid for lack of enablement.

C. Ground 3: The Challenged Claims Are Obvious Over Gao In View of Clark and Irving

For the reasons set forth below, the Challenged Claims are invalid as obvious under 35 U.S.C. § 103(a) in view of the Gao, Clark and Irving references.

1. Overview of Obviousness Based on Gao, Clark and Irving

U.S. Patent. Publication No. 2010/0316646 ("Gao")[6] discloses the use of anti-TIGIT antibodies for therapeutic use; however, Gao uses an alias, "zB7R1," for TIGIT.[7] Gao teaches that "a reagent that blocks zB7R1-CD155 interaction, including ***blocking antibodies*** to either molecule, or soluble forms of either protein, will facilitate T and NK cell responses to the tumor by eliminating or minimizing the inhibitory signal through zB7R1." Ex. 1043 at [0015]; Ex. 1002 ¶¶231, 36. Gao also explicitly teaches that anti-TIGIT agents can be synergistically combined with other agents such as PD-1 inhibitors:

> It is further contemplated that the subject compositions [anti-TIGIT agents] and methods may be ***synergistically combined with immunotherapies*** based on modulation of

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[6] Gao published on December 16, 2010 and is therefore prior art to the '836 patent under 35 U.S.C. §102(a). Ex. 1043.

[7] The receptor zB7Rl was identified as PRO52254 in WO 2004/024068, and now known under several different names including TIGIT and VSTM3. Genentech does not dispute that zB7R1 and TIGIT refer to the same receptor. *See, e.g.*, Ex. 1044 at 3:9 ("WO2006/124667 describes anti-zB7R1 (TIGIT) antibodies which inhibit proliferation of T cells."); *see also* Ex. 1002 ¶¶231-32.

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> other T cell costimulatory pathways, and with ICOS***, PD-1***, CTLA-4 and/ or BTLA modulation in particular.

Ex. 1043 at [0067-688]; Ex. 1002 ¶238.

Although cited on the face of the ’836 patent, Gao was not addressed substantively during prosecution, and there is no indication that the Examiner considered Gao’s teaching of synergistically combining anti-TIGIT agents with PD-1 axis inhibitors. The Examiner relied instead on the Maecker reference that disclosed co-administration of an anti-PD-1 agent with a second inhibitory agent, but, as noted by the Examiner, “does not specifically exemplify a TIGIT antagonist as the second agent.” Ex. 1004 at 618. The Gao reference provides the teaching of using a TIGIT antagonist as the second agent with an PD-1 agent.

Gao taught the use of anti-TIGIT antibodies as preferred agents. U.S. Patent Publication No. 2009/0258013 (“Clark”)[8] further disclosed an anti-TIGIT blocking antibody, designated as 10A7. Ex. 1045 at [0056], [00145]; Ex. 1002 ¶¶239-40. Notably, the 10A7 antibody disclosed in the Clark reference is also the sole anti-TIGIT antibody described in the ’836 patent that meets the functional requirements of the Challenged Claims. Ex. 1002 ¶¶240-41. Consistent with Gao, Clark also

[8] Clark published on October 15, 2009 and is therefore prior art to the ’836 patent under 35 U.S.C. §102(a). Ex. 1045.

explained that antagonistic anti-TIGIT antibodies can block TIGIT-induced inhibition of T cell proliferation for the treatment of cancers. Ex. 1045 at [0056], [0091]; Ex. 1002 ¶241-43.

Gao similarly taught the use of immunotherapies based on the PD-1 pathway. U.S. Patent Publication No. 2010/0203056 ("Irving")[9] further disclosed anti-PD-L1 antibodies which inhibit the immunosuppressive signal of PD-1 for use as an anti-cancer therapeutic:

> In the treatment of cancer, any of the previously described conventional treatments for the treatment of cancer immunity may be conducted, prior, subsequent or simultaneous with the administration of the anti-PD-L1 antibodies of the invention. Additionally, the anti-PD-L1 antibodies of the invention may be administered [sic] prior, subsequent or simultaneous with conventional cancer treatments, such as the administration of tumor-binding antibodies (e.g., monoclonal antibodies, toxin-conjugated monoclonal antibodies) and/or the administration of chemotherapeutic agents.

Ex. 1043 at [0429]; *see also id.* at [0005] and [0040]; Ex. 1002 ¶¶245-46. One of the anti-PD-L1 antibodies disclosed by the Irving reference is clone YW243.55S70,

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[9] Irving published on August 12, 2010 and is therefore prior art to the '836 patent under 35 U.S.C. §102(a). Ex. 1046.

which is also one of the anti-PD-L1 antibodies described in the ’836 patent. Ex. 1046 at [0545]; Ex. 1001, 7:34-36.

For the reasons set forth in more detail below, the Challenged Claims are obvious over the disclosures of Gao, Clark and Irving.

2. The Combination of Gao, Clark and Irving Discloses Every Limitation of the Challenged Claims

(a) Claim 1 and 3

(i) “A method of treating …”/“A method of increasing, enhancing, or stimulating …”

Claim 1 is directed to a “method of treating or delaying progression of a cancer in an individual.” Ex. 1001, 135:52-53. Claim 3 differs from claim 1 only in that it is directed to a “method of increasing, enhancing, or stimulating an immune response or function in an individual.” *Id.* 136:57-58. Both limitations are disclosed by the prior art references Gao, Clark and Irving. Ex. 1002 ¶¶254-55, 283-84.

With regard to the treatment of cancer, Gao discloses “[t]he zB7R1 antibodies, and soluble zB7R1 receptors of the present invention” can be used “in the treatment of specific human diseases such as cancer.” Ex. 1043 at [0015]. Clark discloses “the invention can be used in immunoadjuvant therapy for the treatment of tumors (cancer).” Ex. 1045 at [0241]. Irving discloses that “the anti-PD-L1 antibodies of the invention” may be used “[i]n the treatment of cancer.” Ex. 1046 at [0429]; Ex. 1002 ¶¶ 253-56.

With regard to stimulating an immune response or function in an individual, each of the disclosures demonstrating treatment of cancer also disclose a method of stimulating an immune response. Ex. 1002 ¶¶277-81. In addition, Gao discloses "methods for ***increasing a host immune response*** to antigenic stimulation…." Ex. 1043 at [0044]. Clark discloses "[m]olecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial." Ex. 1045 at [0009]. Irving teaches "anti-PD-L1 antibodies, nucleic acid encoding the same, therapeutic compositions thereof, ***and their use enhance T-cell function*** to upregulate cell-mediated immune responses and for the treatment of T cell dysfunctional disorders, including infection (e.g., acute and chronic) and tumor immunity." Ex. 1046 at Abstract.

(ii) "the method comprising administering to the individual an effective amount of"

Claims 1 and 3 both require "the method comprising administering to the individual an effective amount of" the claimed composition. Ex. 1001, 132:53-54, 136:59-60. Each of Gao, Clark and Irving describe the use of an effective amount of the compositions disclosed for the treatment of cancer or stimulating an immune response. Ex. 1002 ¶263.

Gao discloses "[f]or purposes of therapy, soluble ZB7R1 or anti-ZB7R1 antibody molecules and a pharmaceutically acceptable carrier are administered to a patient in a therapeutically effective amount." Ex. 1043 at [0361]. Gao further

specifies "[t]herapeutic doses [of the zB7R1 antibodies] will generally be in the range of 0.1 to 100 mg/kg of patient weight per day, preferably 0.5-20 mg/kg per day." *Id.* at [0365]; *see also* Ex. 1002 ¶259.

Clark teaches that "a 'therapeutically effective amount' is a concentration or amount of a polypeptide and/or agonist/antagonist which is effective for achieving a stated therapeutic effect." Ex. 1045 at[0133]; *see also* Ex. 1002 ¶260.

Irving discloses that "the invention provides for a method of enhancing T-cell function comprising administering an ***effective amount*** of any of the above described anti-PD-L1 antibodies or compositions." Ex. 1046 at [0037]; Ex. 1002 ¶¶261-62.

(iii) "(i) a PD-L1 binding antagonist …, a PD-1 binding antagonist …, or a PD-L2 binding antagonist …"

Claims 1 and 3 recite three alternative PD-1 axis binding antagonists, including "a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1 and/or B7-1" and "a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2." *See, e.g.*, Ex. 1001, 135:56-57; Ex. 1002 ¶264. Irving discloses that "[t]he anti-PD-L1 antibodies of the invention block the signaling through PD-1 so as to restore a functional response by T-cells from a dysfunctional state to antigen stimulation." Ex. 1046 at [0178]; Ex. 1002 ¶264. Specifically, clone "YW243.55S70 was selected as the primary candidate to pursue based on its ability

to block binding of both human and mouse PD-L1 to PD-1. *Id.* at [0545]. This same clone is one of the anti-PD-L1 antibodies described in the '836 patent. Ex. 1001, 7:34-36.

Additionally, Gao discloses that the disclosed anti-TIGIT antibodies can be used synergistically with PD-1 immunotherapies. Ex. 1043 at [0068]; Ex. 1002 ¶266.

(iv) "(ii) an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof"

Claims 1 and 3 require "an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof." *See, e.g.*, Ex. 1001, 135:59-62. Clark discloses this limitation. Ex. 1045 at [0145]; *see* Ex. 1002 ¶¶267-76.

Clark discloses the same two anti-TIGIT antibodies disclosed in the '836 patent—clones 10A7 and 1F4. Ex. 1045 at [0145]. Clark describes clone 10A7 as a blocking anti-TIGIT antibody but does not use similar language for antibody 1F4. *Id.* at [0056],[0145], Fig. 21. A POSA therefore would have a strong reason to select clone 10A7. Ex. 1002 ¶269.

Clone 10A7 has the claimed functional properties, specifically the ability to bind TIGIT and to block the interaction of CD226 with TIGIT. This is demonstrated by Examples 9 and 14 of the '836 patent. Ex. 1002 ¶¶272-73. Example 14, which

utilizes blocking antibody 10A7, purportedly shows that the "[t]he addition of anti-TIGIT to the cell cultures significantly reduced the ability of TIGIT and CD226 to associate (FIG. 29H)." Ex. 1001, 108:28-31; Ex. 1002 ¶¶274-75. Thus, Clark's disclosure of clone 10A7 inherently discloses "an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof."

(b) Claim 4

Claim 4 depends from claims 1, 2, and 3 and further recites "administering at least one chemotherapeutic agent." Ex. 1001, 137:1-3. Gao, Clark, and Irving disclose this limitation. Ex. 1002 ¶¶285. Specifically, Gao discloses that the zBR7R1 antibodies "will commonly be administered over a period of up to 28 days following chemotherapy or bone-marrow transplant." Ex. 1043 at [0356]; Ex. 1002 ¶286. Clark discloses "TIGIT antagonists and/or antagonists of the TIGIT-PVR signaling interaction (i.e., PVR antagonists) may be administered as adjuvants, alone or together with a growth regulating agent, cytotoxic agent or chemotherapeutic agent, to stimulate T cell proliferation/activation and an antitumor response to tumor antigens." Ex. 1045 at [0241]; Ex. 1002 ¶287. Irving discloses that "the PD-L1 antibody or composition is combined with a treatment regimen further comprising a traditional therapy selected from the group consisting of: … chemotherapy." Ex. 1046 at [0040]; Ex. 1002 ¶288.

(c) Claim 5

Claim 5 depends from claim 3 and further requires "wherein the individual has a cancer." Ex. 1001, 135:4-5. Gao discloses "[t]he zB7R1 antibodies, and soluble zB7R1 receptors of the present invention, can be used to modulate, agonize, block, increase, inhibit, reduce, antagonize or neutralize the activity of either zB7R1 or its counter receptor(s) (i.e. CD155) in the treatment of specific human diseases such as cancer." Ex. 1043 at [0015]; Ex. 1002 ¶290. Clark discloses that "the invention can be used in immunoadjuvant therapy for the treatment of tumors (cancer)." Ex. 1045 at [0241]; Ex. 1002 ¶291. Irving's Example 8, titled "PD-L1 Blockade in Cancer," "present[s] an experiment demonstrating the impact of blocking PD-L1 on orthotopic tumor growth of MC38.Ova murine colorectal carcinoma cells in syngeneic C57B6 mice." Ex. 1046, at [0594]-[0595]; Ex. 1002 ¶293.

(d) Claim 6

Claim 6 depends from claim 1 or claim 5 and further requires "wherein the cancer has elevated levels of T cell infiltration." Ex. 1001, 137:6-7. Clark discloses that "TIGIT expression correlates with immune cell infiltrate in breast cancer tumors." Ex. 1045 at [0241]; Ex. 1002 ¶295. Clark further teaches elevated levels of T cell infiltration, stating that "TIGIT overexpression in tumor immune infiltrate

cells may be aberrant, since decreased T cell activity in tumors would be undesirable." *Id.*; Ex. 1002 ¶¶295-96.

Irving explains "that many tumors exploit expression of PD-1 ligands as a means to attenuate anti-tumor T cells responses. Several human cancers have been characterized to express elevated levels of PD-L1 on both tumors and tumor-***infiltrating leukocytes*** and this elevated PD-L1 expression is often associated with a worse prognosis. Mouse tumor models demonstrate similar increases in PD-L1 expression within tumors and demonstrate a role for the PD-1/PD-L1 pathway in inhibiting tumor immunity." Ex. 1046 at [0594]. Leukocytes include T cells. Ex. 1002 ¶299. Thus, a POSA would understand that cancers with increased T cell infiltration is tied to PD-L1 expression and the PD-1/PD-L1 pathway. Ex. 1002 ¶¶297-300.

(e) Claim 7

Claim 7 depends from claims 1, 2 or 3 and further requires "wherein the inhibitory anti-TIGIT antibody or antigen-binding fragment thereof is a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, or an immunotoxin." Ex. 1001, 137:9-13. Gao and Clark further disclose this limitation. Ex. 1002 ¶300. Gao states that "[e]xemplary antibodies include … ***humanized antibodies*** derived from murine monoclonal antibodies." Ex. 1043 at [0025]; *see also id.* at [0109], claim 2; Ex. 1002 ¶301. Clark discloses that "[i]n one

aspect, an antibody or antigen-binding fragment thereof of the invention is selected from a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, and an immunotoxin." Ex. 1045 at [0017]; *see also* Ex. 1002 ¶¶301-04.

(f) Claims 8 and 9

Claim 8 depends from claims 1, 2 and 3 and further limits the "the PD-L1 binding antagonist" to "an anti-PD-L1 antibody." Ex. 1001, 137:14-15. Claim 9 depends from claim 8 and further requires that "the anti-PD-L1 antibody" contain certain amino acid sequences. *Id.* 137:14-138:3. Irving discloses an anti-PD-L1 antibody with the specific amino acid sequences of claim 9:

> [T]he invention provides for an anti-PD-L1 antibody comprising a heavy chain and a light chain variable region sequence, wherein:
> (a) the heavy chain further comprises and HVR-H1, HVR-H2 and an HVR-H3 sequence having at least 85% sequence identity to GFTFSDSWIH (SEQ ID NO:15), AWISPYGGSTYYADSVKG (SEQ ID NO:16) and RHWPGGFDY (SEQ ID NO:3), respectively, or
> (b) the light chain further comprises an HVR-L1, HVR-L2 and an HVR-L3 sequence having at least 85% sequence identity to RASQDVSTAVA (SEQ ID NO:17), SASFLYS (SEQ ID NO:18) and QQYLYHPAT (SEQ ID NO:19), respectively.

Ex. 1046 at [0014]-[0016].[10] Irving also states that the sequence identity may be up to 100% identity to these amino acid sequences. *Id.* at [0016]; Ex. 1002 ¶¶305-11.

(g) Claim 10

Claim 10 depends from claim 1 or 5 and recites wherein the cancer is selected from the group consisting of 25 different cancer types, including colorectal, breast and pancreatic cancers. Ex. 1001, 138:4-13. Gao, Clark and Irving also disclose this limitation. *See* Ex. 1002 ¶¶312-15.

Gao discloses the use of anti-TIGIT antibodies for the treatment of, for example, pancreatic cancer and colon and intestinal cancer. Ex. 1043 at [0319]. Clark discloses "[t]he data provided herein demonstrates that TIGIT expression correlates with immune cell infiltrate in ***breast cancer*** tumors." Ex. 1045 at [0241]. Irving states "FIG. 9A shows a significant reduction in MC38Ova colon carcinoma tumor growth as a result of application of anti-PD-L1 antibody following therapeutic treatment of established tumors." Ex. 1046 at [0049].

(h) Claim 11 and Claim 12

Claims 11 and 12 depend from claims 1, 2 and 3. Claim 11 further requires "wherein the inhibitory anti-TIGIT antibody or antigen-binding fragment thereof

[10] Figure 11 of Irving identifies the antibody having these amino acid sequences as YW243.55S70. Ex. 1046 at Figs. 11A1-3, 11B1-3.

inhibits and/or blocks the ability of TIGIT to disrupt CD226 homodimerization." Ex. 1001, 138:13-16. Claim 12 further requires "wherein the inhibitory anti-TIGIT antibody or antigen-binding fragment thereof inhibits and/or blocks the interaction of TIGIT with CD226, without impacting PVR-CD226 interaction." *Id*. 138:17-20.

As discussed above, Clark discloses the same anti-TIGIT antibody, clone 10A7, that is disclosed in the '836 patent and used for all of the tests establishing the anti-TIGIT antibody's alleged ability to function as recited in claims 11 and 12. As also discussed above, clone 10A7 has the claimed functional properties of the anti-TIGIT antibodies, including the additional properties recited by claims 11 and 12. Ex. 1002 ¶¶320-323. Thus, Clark's disclosure of clone 10A7 inherently discloses an antibody having the functional properties required by claims 11 and 12.

3. A POSA Would Have Been Motivated to Combine Gao, Clark and Irving and Have Had A Reasonable Expectation of Success

A POSA would have been strongly motivated to follow the teachings of Gao by combining an anti-PD-L1 antibody, such as taught in Irving, with the anti-TIGIT antibodies of Gao and Clark to treat individuals with cancer for at least the following reasons. *Id.* ¶324.

First, as described above, Gao expressly teaches administering the combination of an PD-1 axis inhibitor with an anti-TIGIT antibody. *Id.* ¶325. Gao

expressly discloses the combined use of these anti-TIGIT antibodies "may be ***synergistically combined***" with PD-1 antagonists. Ex. 1043 at [0068].

Second, although Gao specifically teaches the use of blocking anti-TIGIT antibodies to treat cancer (Ex. 1043 at [0015]), Gao does not discloses any amino acid sequences for blocking anti-TIGIT antibodies. Ex. 1002 ¶ 326. Clark discloses clone 10A7, which is one of the first known anti-TIGIT antibodies shown to be effective at blocking normal TIGIT activity. *Id.* ¶328; Ex., 1045 [0342]. Moreover, clone 10A7 is the only antibody disclosed in Clark as being a blocking antibody. Ex. 1002 ¶327; Ex. 1045, [0056], [0145]. A POSA therefore would have had a strong motivation to select clone 10A7 as the anti-TIGIT antibody to be used in connection with Gao's teaching to synergistically combine anti-TIGIT antibodies and a PD-1 axis inhibitor.

Third, Irving also expressly teaches that its disclosed anti-PD-L1 antibodies may be "combined with known methods of treatment chronic infection or cancer, either as combined or additional treatment steps or as additional components of a therapeutic formulation." Ex. 1046 at [0425]; Ex. 1002 ¶¶329-31. Irving also teaches the use of combination therapies for the treatment of cancer. It states: "In the treatment of cancer, any of the previously described conventional treatments for the treatment of cancer immunity may be conducted, prior, subsequent or simultaneous with the administration of the anti-PD-L1 antibodies of the invention."

Id. at [0429]. The "previously described conventional treatments" include "immunotherapy." *Id.* at [0428]. Moreover, Irving provide data showing that clone YW243.55S70 "was selected as the primary candidate to pursue based on its ability to block binding of both human and mouse PD-L1 to PD-1." *Id.* at [545]. A POSA therefore would have been motivated to select clone YW243.55S70 when following Gao's teaching to synergistically combine an anti-TIGIT antibody with an PD-1 axis antagonist.

A POSA would have had a reasonable expectation of success that the combined administration of the anti-PD-L1 antibody of Irving and the anti-TIGIT antibodies of Clark and Gao would be effective to treat individuals with cancer. Ex. 1002 ¶333. Additionally, a POSA would have had additional expectation that combining antagonists of the PD-1 axis with antagonists of TIGIT would be successful because it was known that PD-1 and TIGIT were both co-expressed in the same state of exhausted cells. *Id.* ¶334; Ex. 1053 at [4901].

4. Secondary Considerations, Including Alleged Unexpected Synergy, Cannot Rebut the Strong Showing of Obviousness

There are no secondary considerations supporting non-obviousness here. Genentech relied on alleged evidence of unexpected synergy during prosecution. But, as discussed above, the synergy was not unexpected given the prior art teachings. Ex. 1002 ¶335. Indeed, Gao explicitly teaches that anti-TIGIT agents

can be "***synergistically combined***" with immunotherapies based on modulation of PD-1 and other T cell costimulatory pathways. *See id.*; Ex. 1043 at [0068].

Moreover, any attempt to rely on the alleged synergistic results as an unexpected property to rebut obviousness would fail here for the additional reason that any demonstration of such results is far from commensurate in scope with the broad claims in the '836 patent. Ex. 1002 ¶¶336-37. The Federal Circuit has repeatedly stated that "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (concluding that unexpected results "limited to sodium only" were not commensurate in scope with claims to a catalyst having "an alkali metal"); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (quoting *Grasselli*, 713 F.2d at 743); *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) ("The Board also correctly reasoned that the showing of unexpected results is not commensurate in scope with the degree of protection sought by the claimed subject matter…."); *In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) ("Establishing that one (or a small number of) species gives unexpected results is inadequate proof, for 'it is the view of this court that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.' " (quoting *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971))).

Here, the experimental results involved one PD-1 axis binding antagonist (clone 25A1) combined with one anti-TIGIT antibody (clone 10A7) against two types of cancer (colorectal and breast). In contrast, the incredibly broad claims challenged here cover all types anti-TIGIT antibodies that inhibit the interaction between TIGIT and CD226 in combination with all types of PD-1 axis binding antagonists to treat all types of cancers. Ex. 1001, 135:51-138:20. These alleged unexpected results are not commensurate with the scope of the claimed invention. *See* Ex. 1002 ¶¶336-37.

X. CONCLUSION

For the foregoing reasons, Merck respectfully requests cancellation of the Challenged Claims of the ’836 patent.

DATED: January 7, 2021 Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that the foregoing Petition for Post Grant Review of U.S. Patent No. 10,611,836 contains 18,335 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(a).

DATED: January 7, 2021

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Petition for Post Grant Review of U.S. Patent No. 10,611,836 and Exhibits 1001-1097 were served on January 7, 2021 via EXPRESS MAIL to the attorneys of record for U.S. Patent No. 10,611,836 as evidenced on Public PAIR on January 7, 2021, namely:

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