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Paper 75
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DAIICHI SANKYO COMPANY, LIMITED,
Petitioner

v.

ALETHIA BIOTHERAPEUTICS, INC.,
Patent Owner

Case IPR2015-00291
Patent 8,168,181 B2

Before MICHAEL P. TIERNEY, ERICA A. FRANKLIN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

I. INTRODUCTION

A. Background

Daiichi Sankyo Company, Limited ("Petitioner") filed a Petition (Paper 2; "Pet.") to institute an *inter partes* review of claims 1–6, 8–11, and 15–23 of US 8,168,181 B2 (Ex. 1001; "the '181 patent"). Alethia Biotherapeutics, Inc. ("Patent Owner") filed a Patent Owner Preliminary Response. Paper 10 ("Prelim. Resp."). Based on these submissions, we instituted trial on the following ground of unpatentability asserted by Petitioner:

Challenged Claims	Basis	References
1–6, 8–11, 15–23	§ 102(a)	Hiruma[1]

Decision to Institute (Paper 14, "Dec.").

After institution of trial, the Patent Owner filed a Patent Owner Response (Paper 43, "PO Resp."), to which Petitioner filed a Reply (Paper 54, "Pet. Reply").

Petitioner relies upon the Declarations of Dr. Paul R. Crocker ((Ex. 1003 ("Crocker Declaration"); Ex. 1044 ("Reply Crocker Declaration")) and Dr. Michael R. Clark (Ex. 1004) ("Clark Declaration") in support of its Petition.

Patent Owner relies upon the Declarations of Dr. Brendan F. Boyce (Ex. 2074) ("Boyce Declaration"); Dr. Kathryn E. Stein (Ex. 2076) ("Stein Declaration"); Dr. Mario Filion (Ex. 2100) ("Filion Declaration"); and Dr.

[1] Yoshiharu Hiruma et al., WO 2009/048072, published on April 16, 2009. Ex. 1002. The English translation of Ex. 1002 is provided as Ex. 1023.

Gilles Tremblay (Ex. 2101) ("Tremblay Declaration") in support of its Patent Owner Response.

Patent Owner filed a motion to exclude certain of Petitioner's evidence. Paper 60. Petitioner filed an opposition (Paper 64), and Patent Owner filed a reply (Paper 66).

Petitioner filed a motion to exclude certain of Patent Owner's evidence. Paper 63. Patent Owner filed an opposition (Paper 65), and Petitioner filed a reply (Paper 67).

Oral argument was conducted on February 26, 2016. A transcript is entered as Paper 74 ("Tr.").

This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a). We conclude for the reasons that follow that Petitioner has shown by a preponderance of the evidence that claims 1–6, 8–11, and 15–23 of the '181 patent are unpatentable.

B. The '181 Patent (Ex. 1001)

The '181 patent discloses methods of modulating osteoclast differentiation, which may be useful in the treatment of bone loss or bone resorption in patients suffering or susceptible of suffering from certain conditions such as osteoporosis. Ex. 1001, 7:4–8, 7:41–62.

Independent claims 1 and 15 of the '181 patent are illustrative of the challenged claims and provide as follows:

> 1. A method of impairing osteoclast differentiation in a mammal in need thereof, the method comprising administering an antibody or antigen binding fragment which specifically binds to human Siglec-15 (SEQ ID NO.:2) or murine Siglec-15 (SEQ ID NO.:108) to said mammal.

> 15. A method for inhibiting bone resorption comprising administering to a subject in need thereof, an antibody or antigen binding fragment which specifically binds to human Siglec-15 (SEQ ID NO.:2) or murine Siglec-15 (SEQ ID NO.:108).

Challenged claims 2–6 and 8–11 depend from claim 1, either directly or indirectly. Challenged claims 16–23 depend from claim 15, either directly or indirectly.

II. ANALYSIS

A. Claim Interpretation

The parties agree that a claim construction under either a *Phillips* interpretation or broadest reasonable interpretation would not impact the scope of the claim. Tr. 7, 23; *see Phillips v. AWH Corp*., 415 F.3d 1303 (Fed. Cir. 2005). Based upon the facts presented, we determine that the explicit construction of any specific claim term is unnecessary to reach our decision in this case. *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Asserted Ground of Unpatentability: Anticipation of Claims 1–6, 8–11, and 15–23 by Hiruma

Petitioner contends that claims 1–6, 8–11, and 15–23 of the '181 patent are anticipated by Hiruma. Pet. 34–56. Hiruma discloses the amino acid sequence of human Siglec-15 (SEQ ID NO: 2) and mouse Siglec-15 (SEQ ID NO: 4). Ex. 1023, 20:2–14. Hiruma discloses antibodies that specifically recognize human or mouse Siglec-15 and inhibit osteoclast formation and/or osteoclastic bone resorption. *Id.* at 5:1–20, 56:24–58:4,

claim 33; Ex. 1003 ¶ 19. Examples 17, 19–26, and 35 of Hiruma disclose the results of experiments showing the inhibitory effect of Siglec-15 antibodies on osteoclast differentiation. Ex. 1023, 103:19–105:13, 106:17–119:4, 138:3–139:15; Ex. 1003 ¶¶ 19–20. Example 37 of Hiruma discloses the results of an experiment showing the use of a Siglec-15 antibody for inhibiting bone resorption. Ex.1023, 141:10–144:22. Hiruma further discloses administering a Siglec-15 antibody for the purposes of inhibiting or neutralizing the biological activity of Siglec-15 (i.e., the differentiation and/or maturation of osteoclasts). *Id.* at 56:24–59:7, 11:3–5, 5:1–7:1, 17:5–8, Fig. 36, claim 33; Ex. 1003 ¶ 23; Ex. 1004 ¶¶ 31, 33–34.

In support of its assertion that Hiruma teaches each element of claims 1–6, 8–11, and 15–23, Petitioner sets forth the foregoing teachings of Hiruma and provides a detailed claim chart explaining how each claim limitation is disclosed. Pet. 36–40.

We credit the testimony of Dr. Crocker and Dr. Clark that Hiruma describes an antibody or a functional fragment thereof that specifically recognizes Siglec-15 and inhibits osteoclast formation and/or osteoclast bone resorption Ex. 1003 ¶¶ 19–25; Ex. 1004 ¶¶ 31–34

Patent Owner does not dispute that Hiruma discloses the limitations recited in the challenged claims. Rather, a first dispute between the parties is whether the challenged claims of the ’181 patent, filed on October 16, 2009, are entitled to its priority claim as a continuation-in-part to WO 2007/093042 (Ex. 1010) (“Parent Application”), filed on February 13, 2007. PO Resp. 17–60. Without the benefit of priority, Hiruma, a PCT Publication published in Japanese on April 16, 2009, becomes available as prior art to the ’181 patent under 35 U.S.C. § 102(a).

The second dispute between the parties is whether Patent Owner can successfully antedate Hiruma, thus removing the reference as prior art under 35 U.S.C. § 102(a). *See* 35 U.S.C. § 102(g) (2011); *Mahurkar v. C.R. Bard, Inc*., 79 F.3d 1572, 1576 (Fed. Cir. 1996) ("Thus, under section 102(a), a document is prior art only when published before the invention date.").

Accordingly, the question of whether Hiruma anticipates the challenged claims rests on our determination of 1) whether the challenged claims are entitled to the benefit of priority to the Parent Application, and/or 2) whether Hiruma is prior art under 35 U.S.C. § 102(a).

C. The '181 Patent Priority Claim

To be entitled to the benefit of a parent application, one requirement is that the invention claimed must have been disclosed in the parent application in the manner provided by 35 U.S.C. § 112, ¶ 1. *See* 35 U.S.C. § 120; *In re Lukach*, 442 F.2d 967, 968–69 (CCPA 1971). Section 112, ¶ 1, contains both a written description requirement and an enablement requirement. *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co*., 598 F.3d 1336, 1344–55 (Fed. Cir. 2010) (*en banc*). That is, a patent specification must describe the invention sufficiently so that one of ordinary skill in the art would understand that the inventor was in possession of the claimed subject matter and, separately, must teach one of ordinary skill in the art how to make and use the invention. *Id.*

Petitioner contends that the challenged claims are neither adequately described nor enabled and thus not entitled to an earlier priority claim. Pet. 9–34; Pet. Reply 2–18. Patent Owner disagrees. PO Resp. 17–60.

After considering the parties' arguments and evidence of record, we conclude that the Parent Application fails to enable a person of ordinary skill in the art to make and use the invention and further fails to adequately describe the subject matter of the challenged claims. Accordingly, the challenged claims are not entitled to the benefit of priority to the Parent Application. Our reasoning follows.

1. Whether the Parent Application Enables the Challenged Claims

Whether a claim is invalid for lack of enablement is a question of law. *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). The enablement requirement is set forth in 35 U.S.C. § 112, ¶ 1, and provides, in pertinent part, that the specification shall describe "the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the [invention]."

The enablement requirement is met when one skilled in the art, having read the specification, could practice the invention without "undue experimentation." *Cephalon*, 707 F.3d at 1336. When determining whether undue experimentation would be required, courts may consider: "(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). These factors "are illustrative, not mandatory." *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

We consider each of the *Wands* factors in view of the argument and evidence of record.

a. The nature of the invention and breadth of the claims

The claims recite methods for impairing osteoclast differentiation (claims 1–6, 8–11) or inhibiting bone resorption in subjects in need of such treatment (claims 15–23). The methods are carried out by the administration of any antibody or antigen binding fragment that specifically binds to human Siglec-15 to produce the desired therapeutic effect. Thus, the claims require the recited antibody to have a desired therapeutic effect when administered to subjects for the purposes of medical treatment. PO Resp. 51 ("These claims cover anti-Siglec-15 antibodies generated for therapeutic purposes, including those that have or are reasonably likely to have a measurable effect on osteoclast differentiation *in vivo* as measured in a correlative *in vitro* bioassay."); Ex. 1003 ¶ 9; Ex. 1004 ¶ 23.

b. Relative skill of those in the art

The parties generally agree that there was a high level of knowledge and skill in the field of antibodies. Specifically, a person of ordinary skill in the relevant art would have at least a Ph.D. in the field of bone biology, immunology, molecular biology, or related field and have at least 1–2 years of experience in antibody development. PO Resp. 48, Ex. 2074 ¶ 7; Ex. 2076 ¶ 6; Ex. 1003 ¶ 7; Ex. 1004 ¶ 13.

c. The state of the prior art

It was known that the biological process of bone remodeling is regulated by the activities of two principal cell types: osteoblasts and

osteoclasts. Ex. 1010, 1–2. Osteoblasts are responsible for bone formation and osteoclasts are responsible for bone resorption or degradation. *Id.* In the biological process of bone remodeling, osteoclasts remove damaged bone and osteoblasts restore bone. Ex. 2074 ¶ 8; Ex. 1010, 1–5. Disruption of the bone remodeling process occurs during aging and from various bone diseases. Ex. 2074 ¶ 8–9. It was known that impairing osteoclast differentiation or inhibiting bone resorption could prevent bone destruction and provide therapeutic benefit in certain bone diseases. Ex. 2074 ¶¶ 8–9; Ex. 1010, 1–5. For example, at the time of the filing of the Parent Application, the monoclonal antibody denosumab, which binds to Receptor Activator of Nuclear Factor Kappa-B Ligand ("RANKL") to inhibit osteoclast formation, was in phase III clinical trials for treating bone disease. Ex. 2074 ¶¶ 9–11, 16–17, 28.

It was known that Siglec-15 was likely a cell surface protein. PO Resp. 11 (citing Nakamura[2]; Ex. 2074 ¶¶ 17–21 ("[O]ne of ordinary skill in the art would have recognized that AB0326 was likely a cell surface protein."); Ex. 2076 ¶¶ 29, 34–42); Pet. Reply 15. However, prior to the filing of the Parent Application, it was not known that Siglec-15 was a protein specifically upregulated in osteoclasts and thus a potential key regulator of osteoclast differentiation. PO Resp. 11–12; Ex. 1010, 1–5; Ex. 2074 ¶¶ 12–21.

It was known that "'one could obtain an antibody to specifically bind to any particular target antigen through routine use of those well-developed

[2] Yusuke Nakamura et al., US 2004/0076992, published April 22, 2004. Ex. 2065.

methods long before 2007.'" PO Resp. 21 (quoting Ex. 2076 ¶ 16); Ex. 2076 ¶ 48; Ex. 2076 ¶ 20; Ex. 2074 ¶¶ 27–29. We note, however, that producing an antibody to an antigen is distinct from producing an antibody to that same antigen having a desirable therapeutic effect. Ex. 2075, 273:15–274:24.

d. The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970).

The Parent Application disclosed Siglec-15 (referred to as "AB0326"), including both the gene and protein sequences of Siglec-15. Ex. 1010, 89 (SEQ ID NOS.: 1 and 48, respectively). The Parent Application discloses Siglec-15 as a protein that is specifically upregulated in osteoclasts. Ex. 1010, 70:26–29 (The Siglec-15 gene "is markedly upregulated in intermediate and mature osteoclast compared to precursor cells," and thus "this gene may be required for osteoclastogenesis and/or bone remodeling."); Ex. 2074 ¶¶ 12–15.

The Parent Application disclosed that inhibiting expression of Siglec-15 using a short hairpin RNA (shRNA) knockdown assay impaired formation of osteoclasts from precursor cells. Ex. 1010, 84–85, Fig. 35. The Parent Application further disclosed that Siglec-15 is capable of restoring the osteoclastogenesis capabilities of the model cell line. Ex. 1010, 87:9–31. We are persuaded that both studies would have indicated to a person of ordinary skill in the art that inhibiting Siglec-15 can potentially impair formation of osteoclasts from precursor cells. Ex. 2074 ¶¶ 9–15, 26,

41; Ex. 2058, 86:2–17; 87:16–88:10; Ex. 1003 ¶ 17.

The Parent Application provides a general disclosure regarding inhibitory compounds to osteoclast differentiation, but does not expressly disclose anti-Siglec-15 antibodies that can inhibit bone resorption or impair osteoclast differentiation. Ex. 1010, 30:30–33; Pet. 19–21 (citing Ex. 1003 ¶¶ 7, 17, 18; Ex. 1004 ¶¶ 7, 8, 12, 13, 16, 21, 23); Pet. Reply 2–3 (citing Ex. 1045 at 90:25–91:6, 96:19–97:9); PO Resp. 12–13. The Parent Application, however, provides a general disclosure of known methods for making antibodies against a target protein. Ex. 1010, 35–44; Ex. 2058, 95:18–22; Ex. 2075, 25:2–10, 28:22–29:4; Ex. 2076 ¶ 31; Ex. 2074 ¶ 27; Ex. 2076 ¶ 31.

The Parent Application does not disclose any structural information regarding an antibody that binds Siglec-15 or any epitopes or unique antigenic regions useful for generating antibodies having the desired functional properties. Ex. 1004 ¶¶ 16, 17, 23, 25; *cf.* Ex. 2076 ¶ 19 ("To perform these conventional methods to develop an antibody with desired activity by 2007, one would *not* need to determine the precise mechanism of action (of the protein or antibody), the specific epitope target on the protein, or the amino acid sequence of the antibody.").

The Parent Application discloses functional assays, including an osteoclastogenesis assay, that may be used to screen for and identify agents, including antibodies, that inhibit the differentiation of osteoclast precursor cells via their association with Siglec-15. Ex. 1010, 61:28–62:23, 86:1–3; Ex. 2074 ¶¶ 10–11, 27–29. The disclosed osteoclastogenesis assay, however, is an *in vitro* assay, which may not reflect how an antibody would behave *in vivo*. Ex. 1004 ¶ 27. For example, an epitope to which an

antibody binds *in vitro* may not be available when the protein is folded into its *in vivo* conformation. Ex. 1004 ¶¶ 20, 27; Ex. 1044 ¶ 10.

e. The presence or absence of working examples

The Parent Application contained no working example of a Siglec-15 antibody having the desired biological properties.

f. The predictability or unpredictability of the art

In cases involving unpredictable factors, the scope of enablement varies inversely with the degree of unpredictability of the factors involved. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Here, the art involves therapeutically regulating the biological process of bone remodeling, the successful completion of which necessitates laboratory research, clinical studies, and other trial-and-error experimentation. The evidence of record supports a finding that the prior art was at least somewhat unpredictable. Ex. 2075, 82–106.

g. The quantity of experimentation necessary

The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. *Atlas Powder Co., v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Patent Owner argues that any experimentation needed to make and use the claimed antibodies would have been routine. PO Resp. 46–59, citing *In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening."). In particular, Patent Owner contends that anti-Siglec-15

antibodies could have been made without undue experimentation using conventional techniques known in the art. PO Resp. 47. Petitioner does not appear to dispute this point. Pet. Reply 12–14.

What is disputed is whether the functional assays disclosed in the Parent Application to identify antibodies with a particular function would have been considered routine screening or "undue" experimentation. In this regard, Patent Owner argues that the osteoclastogenesis assay disclosed in the Parent Application "was a well-known and robust assay in 2007 to demonstrate osteoclast differentiation function, to identify regulators (e.g., inhibitors) of osteoclast differentiation and bone resorption, and to correlate and reliably predict *in vivo* osteoclast and bone resorptive activity." PO Resp. 47–48 (citing Ex. 2074 ¶¶ 10–11, 28–29; Ex. 2058, 93:20–95:3, 181:4–9; Ex. 2075, 100:10–18, 101:17–102:1).

Petitioner contends that the Parent Application is a research plan or an invitation for further experimentation. Pet. 26 (citing Ex. 1004 ¶ 26). Specifically, Petitioner contends that the osteoclastogenesis assay disclosed in the Parent Application "is, at best, a screening tool for any number of inhibitors, not necessarily antibodies, of osteoclast differentiation," and "by no means is this assay an indication that a therapeutic Siglec-15 antibody even could be made, much less a recipe for actually making such a therapeutic antibody." *Id.* at 29 (citing Ex. 1004 ¶ 27). Petitioner further contends that "the amount of experimentation required to identify such an antibody would be excessive, at least because it is uncertain whether such an antibody could even be made." *Id.* at 27 (citing Ex. 1004 ¶¶ 7, 11, 13, 17, 28).

h. Discussion

The central enablement issue in this case is whether the development of antibodies having the desired function would have required undue experimentation. In view of the forgoing, we find that practicing the methods of the challenged claims at the time of the filing of the Parent Application would have required excessive experimentation, even if routine. *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).

In this case, the Parent Application discloses a potential target for drug development (i.e., Siglec-15), an assay by which to screen potential inhibitory compounds to osteoclast differentiation, and a general description pertaining to conventional methods of producing antibodies. Thus, to arrive at the invention of the challenged claims, a person of ordinary skill in the art would have had to choose to pursue anti-Siglec-15 antibodies as a potential inhibitor to test in the disclosed osteoclastogenesis assay, generate anti-Siglec-15 antibodies, and then screen those antibodies until an antibody having the desired biological properties was identified. Ex. 1045, 48:18–50:6; Ex. 2075, 82–106. We note the considerable amount of time, skill and labor necessary to practice the invention and the uncertainty as to whether antibodies having the desired therapeutic properties could be achieved. Ex. 1004 ¶¶ 7, 11, 13, 17, 20, 27–28; Ex. 1044 ¶ 10; Ex. 2075, 82–106.

The Parent Application discloses Siglec-15 can potentially impair formation of osteoclasts from precursor cells. Ex. 2074 ¶¶ 9–15, 26, 41; Ex. 2058, 86:2–17; 87:16–88:10; Ex. 1003 ¶ 17. However, the Parent Application fails to provide sufficient detailed guidance to a person of ordinary skill in the art suggesting more than a mere starting point or direction for further research. For example, the Parent Application discloses

the protein sequence of Siglec-15, but offers no credible guidance as to unique antigenic regions or epitopes in Siglec-15 that would have been useful for generating antibodies having the required functional properties. While epitope mapping may not be required to screen antibodies (Ex. 2076 ¶ 19), the lack of such specific guidance would have required a person of ordinary skill in the art to engage in a complicated and lengthy screening process to practice the invention. Ex. 1004 ¶¶ 7, 11, 13, 17, 20, 27–28; Ex. 1044 ¶ 10; Ex. 2075, 82–106. That is, one of ordinary skill "would have been required to engage in an iterative, trial-and-error process to practice the claimed invention even with the help of the . . . specification." *ALZA Corp.*, 603 F.3d at 943.

Accordingly, undue experimentation was required to practice the methods claimed in the '181 patent based on the specification of the Parent Application. "The amount of required experimentation [to satisfy the enablement requirement] . . . must be reasonable." *White Consol. Indus., Inc. v. Vega Servo-Control, Inc.*, 713 F.2d 788, 791 (Fed. Cir. 1983).

2. Whether the Parent Application Provides Adequate Written Description for the Challenged Claims

Adequacy of the written description is a question of fact. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to 'recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.'" *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003), *quoting Vas–Cath Inc. v. Mahurkar*, 935 F.2d

1555, 1561.

The question before us is whether the Parent Application provides adequate written description support for a genus of antibodies having the desired functional properties required to practice the claimed method—the ability to inhibit osteoclast differentiation (claims 1–6, 8–11) or the ability to inhibit bone resorption (claims 15–23). Pet. 11–24. We conclude that the Parent Application fails to provide adequate written description support for the challenged claims. Our reasoning follows.

Patent Owner contends that the Parent Application fully characterizes Siglec-15 as an antigen, which is sufficient to provide adequate written description support to an antibody that binds the antigen. PO Resp. 19–21 (quoting *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) ("As long as an applicant has disclosed a '*fully characterized antigen*,' either by its structure, formula, chemical name, or physical properties . . . , the applicant can then claim an antibody by its binding affinity to that described antigen.")). Patent Owner refers to this legal principle as "the antibody rule" and further notes that "[t]his antibody rule has been incorporated into the USPTO's examiner training materials on written description since at least 2001." *Id.* at 19 (siting Ex. 2077[3] (Example 13); Ex. 2078[4] (Example 16)).

We are not persuaded by this reasoning. The challenged claims contain functional claim language concerning the biological properties of the recited antibody. The Federal Circuit, however, has on several occasions distinguished between claims not involving functional claim language and

[3] USPTO Written Description Training Materials (2008).

[4] Revised Interim Written Description Guidelines Training Materials (2001).

claims that contain functional claim language, such as the claims at issue in the present case. *See e.g., Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011); *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 731 (Fed. Cir. 2014). In *Centocor*, for example, at issue were claims to TNF-α antibodies having particularly desirable therapeutic properties. The court distinguished *Noelle* as follows:

> While [*Noelle*] suggests that written description for certain antibody claims can be satisfied by disclosing a well-characterized antigen, that reasoning applies to disclosure of newly characterized antigens where creation of the claimed antibodies is routine. Here, both the human TNF-α protein and antibodies to that protein were known in the literature. The claimed "invention" is a class of antibodies containing a human variable region that have particularly desirable therapeutic properties: high affinity, neutralizing activity, and A2 specificity. *Claiming antibodies with specific properties, e.g., an antibody that binds to human TNF-α with A2 specificity, can result in a claim that does not meet written description even if the human TNF-α protein is disclosed because antibodies with those properties have not been adequately described.*

Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1352 (Fed. Cir. 2011) (emphasis added).

In view of the court's logic set out in *Centocor*, we are not persuaded by Patent Owner's arguments that disclosure of Siglec-15 as a fully characterized antigen in the Parent Application, without more, is sufficient to provide adequate written description support for a Siglec-15 antibody that produces a desirable biological activity or therapeutic result.

Patent Owner argues, however, that the Parent Application does provide more. PO Resp. 21–24. Specifically, Patent Owner contends that the Parent Application, in addition to disclosing "extensive characterization

of Siglec-15" in terms of both structure and function, further describes, "in great detail[,] procedures for generating antibodies, such as hybridoma technology, phage display technology and mammal immunization techniques, all of which were well-known." *Id.* at 24 (citing Ex. 2058, 95:18–22; Ex. 2075, 25:2–10, 28:22–29:4; Ex. 2076 ¶ 31; Ex. 2074 ¶ 27); *see also*, *Id.* at 36 ("The [Parent Application] devoted at least seven (7) entire pages to describing techniques for generating antibodies.") (citing Ex. 2076 ¶¶ 30–31; Ex. 1010, 33–40). Patent Owner further notes that the Parent Application "clearly describes using such techniques with well-known osteoclastogenesis assays to generate and identify antibodies that specifically inhibit Siglec-15." *Id.* (citing Ex. 1010, 86:1–3 (disclosing a process "to identify molecules (small molecule drugs, peptides, or antibodies) capable of inhibiting AB0326."); *see also*, *Id.* at 36 (citing Ex. 1010, 61:28–62:23, Example L). Patent Owner further argues that the Parent Application discloses well-accepted osteoclastogenesis assays that are predictive of inhibitory activity *in vivo*. PO Resp. 30–31 (citing Ex. 2074 ¶¶ 10–11, 28–29, 33).

We are not persuaded by the argument and evidence presented by Patent Owner. The Parent Application fails to disclose any species of antibody that impairs osteoclast differentiation or inhibits bone resorption. The Parent Application also fails to provide any specific structural or physical information so as to define a genus of antibodies having the desired therapeutic properties. Patent Owner's arguments merely rely on the identification of Siglec-15 as the antigen and the well-known structure of antibodies in general. As noted by Petitioner, however, the claims do not recite a general antibody, but an antibody having a specific desired activity.

Pet. Reply 7. In this regard, the evidence of record suggests that identification of Siglec-15 itself is insufficient to describe a genus of antibodies that bind to Siglec-15 and produce a desired therapeutic effects. Ex. 1046, 39:5–9 ("In my understanding when antibodies are being generated, some will be inhibitory because they bind specifically to critical parts of the polypeptide and others may not and will not be inhibitory."); Ex. 2075, 117:8–19.

Here, as in *Alonso*, "[t]he specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies implicated by the method." *In re Alonso*, 545 F.3d 1015, 1022 (Fed. Cir. 2008). Accordingly, we determine that the Parent Application fails to sufficiently describe common structural information to show possession to the genus of antibodies recited in the challenged claims. *See Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366–67 (Fed. Cir. 2011) (holding written description inadequate "[g]iven the absence of information regarding structural characteristics of" the claimed genus); *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) (holding that adequate written description requires identification of "structural features commonly possessed by members of the genus that distinguish them from others," allowing one of skill in the art to "visualize or recognize the identity of the members of the genus").

3. Conclusion

In view of the forgoing, we conclude that the claims of the '181 patent are not entitled to the priority date of February 13, 2007. Hiruma is thus

prior art to the ’181 patent and anticipates the challenged claims under 35 U.S.C. § 102(a).

D. Antedating Hiruma

1. Background

Patent Owner attempts to antedate Hiruma. PO Resp. 60–84. An inventor may antedate a prior art reference under 35 U.S.C. § 102(a) if the inventor was the first to conceive of a patentable invention, and then connects the conception of the invention with its constructive reduction to practice by reasonable diligence on the inventor’s part, such that conception and diligence are substantially one continuous act. *Mahurkar v. C.R. Bard, Inc*., 79 F.3d 1572, 1577 (Fed. Cir. 1996).

Hiruma is dated April 16, 2009. Patent Owner contends that the claimed invention of the ’181 patent was conceived prior to April 16, 2009, and constructively reduced to practice on October 16, 2009, the filing date of the ’181 patent. PO Resp. 61, 71. Patent Owner further contends that the inventors were reasonably diligent from April 9, 2009, to the date of the constructive reduction to practice. *Id*. Patent Owner contends that, as a consequence, Hiruma does not qualify as prior art. *Id.*

For support, Patent Owner relies on the Parent Application to demonstrate conception. *Id.* at 63–68. Patent Owner further relies on the declaration testimony of Dr. Mario Filion, who is named as a co-inventor on the ’181 patent. PO Resp. 68–69; Ex. 2100. Dr. Filion testifies that the subject matter claimed in the ’181 patent was conceived prior to February 13, 2007, the filing date of the Parent Application, or alternatively, prior to June 19, 2007, the date in which Dr. Filion presented Patent Owner’s clinical

programs to Petitioner. Ex. 2080 ¶¶ 1–2. Patent Owner additionally provides a copy of the slide deck that accompanied Mr. Filion's presentation to Petitioner. Ex. 2080 ("Patent Owner Presentation").

To show diligence, Patent relies on the declaration testimony of Dr. Dr. Gillis Tremblay (Ex. 2101), who is named as a co-inventor on the '181 patent, and the accompanying Diligence Chart (Ex. 2015), which provides time logs prepared by Dr. Tremblay relating to activities he and his research team performed during the relevant timeframe between April 9, 2009 and October 16, 2009. PO Resp. 71–77; Ex. 2101 ¶ 8.

Petitioner responds, first, by challenging Patent Owner's conception proofs. Pet. Reply 20–25. According to Petitioner, the Parent Application and Patent Owner Presentation amount to a plan to target Siglec-15 for development, which is insufficient to establish conception. *Id.* Second, Petitioner challenges Patent Owner's proofs to show reasonable diligence.

2. Discussion

"Conception requires both the idea of the invention's structure and possession of an operative method of making it." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991), citing *Oka v. Youssefyeh*, 849 F.2d 581, 583 (Fed.Cir.1988). In *Amgen*, the court said:

> Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property . . . because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

927 F.2d at 1206.

The evidence of record does not support Patent Owner's contention that the invention of the challenged claims was conceived prior to the critical date, April 16, 2009, the publication date of Hiruma. As discussed above, the Parent Application does not adequately describe an antibody capable of performing the functions recited in the challenged claims. Such a disclosure is also absent in Patent Owner Presentation, which instead discloses possible directions for development. *See* Ex. 2080, 37 (disclosing "[a] plethora of high-potential targets to self-sustain clinical pipeline."). Thus, neither the Parent Application nor Patent Owner Presentation is sufficient to establish that antibodies that could function in the claimed methods had been defined prior to the critical date. *Amgen*, 927 F.2d at 1206 ("it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it"); Pet. Reply 19–25.

Furthermore, as noted by Petitioner, "the claimed subject matter is recognized as unpredictable and therefore could not have been conceived until it was determined that the antibodies recited in the claims actually worked for their intended purpose as claimed in the methods." Pet. Reply 20 (citing *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001)). In this regard, the weight of the evidence of record suggests that Patent Owner was still conducting trial and error experimentation of the type that the *Alpert* court characterized as evidencing a lack of conception. *Alpert v. Slatin*, 305 F.2d 891, 894 (CCPA 1962). For example, as of April 9, 2009, Patent Owner was in possession of DNA encoding 46 candidate fragment antigen-binding (Fab) sequences identified as binding a Siglec-15 fusion protein. Ex. 2105, 1. To identify antibodies with a therapeutic

function, however, additional characterization and experimentation was necessary. For example, the candidate antibodies were tested *in vitro* to determine their effect on isolated osteoclasts, which did not occur until at least May 15, 2009. PO Resp. 74; Ex. 2105, 7. Subsequent to that experimentation, Patent Owner used epitope mapping, functional characterization of lead sequences, and bioinformatics analysis in its efforts to identify the desired antibodies. PO Resp. 73–76; Ex. 2105, 3, 21–23, 28–29. The information development during this period, after the critical date, was essential to define a class of antibodies by its physical or chemical properties and not solely by its desired biological property. *See Alpert*, 305 F.2d at 894 ("[W]here results at each step [of experimentation] do not follow as anticipated, but are achieved empirically by what amounts to trial and error[,]" "the inventor's mind cannot formulate a completed invention until he finally performs a successful experiment.").

Because Patent Owner's records indicate that critical research activity was still necessary before identifying a Siglec-15 antibody capable of performing the functions recited in the challenged claims, the mental embodiment of such antibodies as of the critical date "was a mere hope or expectation, a statement of a problem, but not an inventive conception." *Id.* There is insufficient conception of an antibody based solely on its proposed or expected biological activity. *See Amgen*, 927 F.2d at 1206 (finding no conception of a nucleic acid based solely on its proposed biological activity). Accordingly, we determine that Patent Owner has failed to establish conception prior to the critical date.

In view of our determination that Patent Owner has not proved conception, we do not need to determine whether Patent Owner adequately

demonstrated diligence, and therefore do not need to reach the issues raised by Patent Owner and opposed by Petitioner.

We conclude, therefore, that Patent Owner has not antedated Hiruma, which is thus prior art under 35 U.S.C. § 102(a).

E. Patent Owner's Motion to Exclude Evidence

Patent Owner's motion filed on January 5, 2016, seeks to exclude portions of Petitioner's expert testimony. Paper 60. Specifically, Patent Owner seeks to exclude 1) paragraphs 14–18 and 20–25 of the Crocker Declaration (*id.* at 1–9); 2) paragraphs 16, 21, 22, 28, and 30–33 of the Clark Declaration (*id.*); and 3) paragraphs 4–9 of the Reply Crocker Declaration (*id.* at 10–15).

We have reviewed the cited portions of the testimony provided by Drs. Crocker and Clark and see no credible basis that would warrant their exclusion. Patent Owner's objections go to the weight and sufficiency of the testimony, rather than its admissibility. We are capable of discerning from the testimony, and the evidence presented, whether the witness' testimony should be entitled to any weight, either as a whole or with regard to specific issues. We weigh such testimony on an issue-by-issue basis, as appropriate. Furthermore, Patent Owner had the opportunity to address any alleged deficiencies in the testimony of Drs. Crocker and Clark in its Patent Owner's Response, and we are capable of weighing that testimony accordingly.

Thus, we deny Patent Owner's motion seeking to exclude the testimony of Drs. Crocker and Clark in this proceeding.

F. Petitioner's Motion to Exclude Evidence

Petitioner seeks to exclude the following: (1) the entirety of the Boyce Declaration; (2) paragraphs 6, 14, 28, and 36 of the Stein Declaration; and (3) Ex. 2152 (Alethia Laboratory Notebook 110). Paper 63.

With regard to the issues raised by Petitioner challenging Patent Owner's submission of the testimony provided by Drs. Boyce and Stein, we have reviewed the cited portions of that testimony and we see no basis for excluding it. Petitioner's objections go to the weight and sufficiency of the testimony, rather than its admissibility. Thus, for the same reasons indicated above, we deny Petitioner's motion seeking to exclude the testimony of Drs. Boyce and Stein in this proceeding.

We find it unnecessary to consider the objections to the admissibility of Exhibit 2152. Paper 63, 10–14. We have not relied upon the details of Exhibit 2152 in reaching our decision. In other words, even without relying on Exhibit 2152, we have determined that Petitioner has demonstrated, by a preponderance of the evidence, that the challenged claims of the '181 patent are unpatentable. Accordingly, the issues raised by Petitioner regarding Ex. 2152 are moot.

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition demonstrates, by a preponderance of the evidence, that claims 1–6, 8–11, and 15–23 are unpatentable under 35 U.S.C. § 102(a) over Hiruma. This is a final written decision of the Board under 35 U.S.C. § 318(a). Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–6, 8–11, and 15–23 of the '181 patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied;

FURTHER ORDERED that Petitioner's Motion to Exclude is denied-in-part and dismissed-in-part.

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