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Elanco US Inc.
Patent Division
2500 Innovation Way
Greenfield, IN 46140

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SKELDING, ZACHARY S

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SARAH RUE, BRENDAN ECKELMAN,
QUINN L. DEVERAUX, and MARC NASOFF

Appeal 2019-005727
Application 15/685,257
Technology Center 1600

Before RICHARD M. LEBOVITZ, FRANCISCO C. PRATS, and JAMIE T. WISZ, *Administrative Patent Judges.*

WISZ, *Administrative Patent Judge.*

DECISION ON APPEAL

STATEMENT OF THE CASE

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 21–23. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

CLAIMED SUBJECT MATTER

The Specification describes reagents and methods for preventing and/or treating canine disease conditions (e.g., lymphoma) and states that "epitopes of canine-CD20 have been identified that may be targeted to deplete canine blood and/or tissues of B cell lymphoma cells." Spec. 1. The Specification further states that "[i]mmunogens have been identified, as described herein, that may be used to induce and/or enhance an immune response (e.g., the production of antibodies) suitable for use in preventing and/or treating these diseases." *Id.* Claim 21 is illustrative of the claimed subject matter and is reproduced below:

> 21. An isolated monoclonal antibody comprising at least one set of variable region amino acid sequences selected from the group consisting of:
>
> a light chain variable region (LC-V) comprising the sequence of DIVMTQAAPSVPVTPGESVSISCRS**X**$_1$K**X**$_2$LLHR**X**$_3$**X**$_4$N TYLYWFLQRPGQSPQLLIYRMSNLASGVPDRFSGSGS GTAFTLRISRVEAEDVGVYYCMQHLEFPFTFGGGTKL EIK (SEQ ID NO.:17) and a heavy chain variable region (HC-V) comprising the sequence of EVQLQQSGPELVKPGASVKISCKASGYTFTDYYNINW

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Elanco Tiergesundheit AG. Appeal Br. 2.

VKQSHGKSLEWIGDINPNNGDTSYNQKFKGKAPL TVDKSSSTAYMEVRSLTSEDSAVYFCARGGVLRYPY YYVMDYWGQGTSVTVSS (SEQ ID NO.: 11);

where X_1 is any amino acid other than asparagine (N) when X_2 is serine (S) or threonine (T);

where X_2 is any amino acid other than S or T when X_1 is N;

where X_3 is an amino acid selected from the group consisting of alanine (A), glutamic acid (E), phenylalanine (F), histidine (H), isoleucine (I), lysine (K), leucine (L), proline (P), glutamine (Q), arginine (R), threonine (T), valine (V) and tyrosine (Y), when X_4 is glycine (G); and

where X_4 is an amino acid selected from the group consisting of A, E, F, H, I, K, L, P, Q, R, V, Y, and tryptophan (W), when X_3 is N;

an LC-V comprising the sequence of DIVMTQAAPSVPVTPGESVSISCRS**X_1**K**X_2**LLHR**$X_3$$X_4$**N TYLYWFLQRPGQSPQLLIYRMSNLASGVPDRFSGSGS GTAFTLRISRVEAEDVGVYYCMQHLEFPFTFGGGTKL EIK (SEQ ID N0.:17) and a HC-V comprising the sequence of EVQLQQSGPELVKPGASVKISCKASGYTFTDYYMNW VKQSHGKSLEWIGDINPN**$X_3$$X_4$**DTSYNQKFKGKAPL TVDKSSSTAYMEVRSLTSEDSAVYFCARGGVLRYPY YYVMDYWGQGTSVTVSS (SEQ ID NO.: 18),

where X_1 is any amino acid other than N when X_2 is S or T;

where X_2 is any amino acid other than S or T when X_1 is N;

where X_3 is an amino acid selected from the group consisting of A, E, F, H, I, K, L, P, Q, R, T, V and Y, when X_4 is G; and

where X_4 is an amino acid selected from the group consisting of A, E, F, H, I, K, L, P, Q, R, V, Y, and W, when X_3 is N;

an LC-V comprising the sequence of DIVMTQAAPSVPVTPGESVSISCRSNKSLLHRNGNTYL YWFLQRPGQSPQLLIYRMSNLASGVPDRFSGSGSGTA

FTLRISRVEAEDVGVYYCMQH LEFPFTFGGGTKLEIK (SEQ ID NO.: 9) and a HC-V comprising the sequence of EVQLQQSGPELVKPGASVKISCKASGYTFTDYYMNW VKQSHGKSLE WIGDINPN**X_3X_4**DTSYNQKFKGKAPL TVDKSSSTAYMEVRSLTSEDSAVYFCARGGVLRYPY YYVMDYWGQGTSVTVSS (SEQ ID NO.: 18);

where X_3 is an amino acid selected from the group consisting of A, E, F, H, I, K, L, P, Q, R, T, V and Y, when X_4 is G; and

where X_4 is an amino acid selected from the group consisting of A, E, F, H, I, K, L, P, Q, R, V, Y, and W, when X_3 is N; and,

an LC-V comprising the sequence of DIVMTQSQKFMSRSVGDRVSVTCKASQNVGPNVA WYQQRPGQSPKPLIYSASYRYSGVPDRFTGSGSGTDF TLTISNVQSEDLAEYFCQQYNNYP YTFGGGTKLEIK (SEQ ID NO.: 13) and a HC-V comprising the sequence of EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYNIHW VKQRPEQGLEWIGWI**X_5X_6**E**X_3X_4**HTKY ASKFQGKATITADTSSNTA YLQLSSLTSEDTA VYYCTSLRHYYGSSYVSPHYYWGQGTTLTVSS (SEQ ID NO.: 19); where X_3 is an amino acid selected from the group consisting of A, E, F, H, I, K, L, P, Q, R, T, V and Y, when X_4 is G;

where X_4 is an amino acid selected from the group consisting of A, E, F, H, I, K, L, P, Q, R, V, Y, and W, when X_3 is N;

where X_5 is any amino acid other than aspartic acid (D); and

where X_6 is any amino acid other than P; and

wherein the antibody binds canine CD20 with an affinity (K_d) of at least 20 nM.

Claims App.

REJECTIONS

The Examiner rejected claims 21–23 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

ISSUES AND ANALYSIS

To satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, the specification must "reasonably convey[] to those skilled in the art that the inventor had possession" of the claimed invention as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written description requirement for a claimed 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." *Id.* at 1350.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. MPEP § 2163. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. *Id.* (citing *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014) (Claims directed to a functionally defined genus of antibodies were not supported by a disclosure that "only describe[d] one type of structurally similar antibodies" that "are not representative of the full variety or scope of the genus.")).

The Examiner finds that claims 21–23 "are drawn to a genus of mutant forms of the anti-C20 1G1 and 1G10 antibodies wherein certain residues in the CDR1 of the light chain (X_1, X_2, X_3, and X_4) and/or the CDR2 of the heavy chain (X_3, X_4, X_5, and X_6) of these antibodies can be

nearly any residue insofar as the mutated 1G1 or 1G10 antibody binds canine CD20 with an affinity (Kd) of at least 20 nM." Ans. 5. The Examiner further finds that

> the genus of potential antibodies encompassed in the claim breadth is enormous involving many millions of potential members and yet the instant specification does not disclose what antibody structure of these many millions of potential variants is critical to the ability of the variant to bind canine CD20 with a Kd of at least 20 nM.

Final Act. 3.

According to the Examiner, the Specification describes the cloning of the 1G1, 1G10, and 1E4 antibodies, as well as variants of the 1E4 antibody. Ans. 5. However, these 1E4 variants are not claimed; rather, mutant, amino-acid substituted forms of 1G10 and 1G1 antibodies are claimed. *Id.* at 8. The Examiner finds that the 1G1, 1G10, and 1E4 antibodies have "notably different CDRs and framework regions and thus appear to be derived from different germline variable domain sequences." *Id.* at 5.

The Examiner also finds that

> showing that one particular antibody - 1E4 - tolerates four particular amino acid changes when such changes are present in four 1E4 variants each having a single change - N33K, G34K, G34Q **or** G34A - does not inform the skilled artisan as to the tolerance/intolerance of the 1E4 antibody or structurally distinct antibody like 1G10 to changes in other CDR residues or to changes in multiple CDR residues.

Id. at 4.

The Examiner also finds that the Specification "does not disclose, and the skilled artisan cannot predict, which particular combinations of X_1, X_2, X_3, X_4, X_5 and X_6 light and heavy chain amino acids contained within the claimed genus of 1G1 and 1G10 mutants are sufficient to support binding to

canine CD20 with a Kd of at least 20 nM." Ans. 15. In fact, the Examiner finds that the Specification "does not reduce to practice any antibodies having any combinations of variant amino acids that bind canine CD20 with an affinity of (Kd) at least 20 nM." *Id.* at 12–13.

> The Examiner concludes that, given:
>
> (i) the notably different CDR and framework sequences of the 1E4, 1G1 and 1G10 antibodies,
>
> (ii) the unpredictability in the art associated with making mutations to multiple residues within a given CDR, and
>
> (iii) the lack of any actual reduction to practice of mutant antibodies having an affinity (Kd) of at least 20 nM encompassed in the breadth of the instant claims,
>
> the skilled artisan would not recognize possession of the claimed genus of antibodies from the teachings of the instant specification.

Ans. 11.

Appellant argues that the Specification contains adequate written description for the variable regions and each of the point mutations claimed. Appeal Br. 10.[2] Specifically, Appellant argues that the Specification adequately discloses "certain residues which can be substituted with certain other amino acids without the loss of antibody function." *Id.* at 11. Appellant also cites to *Ex parte Grosmaire*, Appeal No. 2017-006468 (PTAB Oct. 10, 2018) as evidence of the Board finding that the written description requirement is satisfied even when antibodies are claimed only by their six CDR sequences. *Id.*

[2] The Appeal Brief does not include page numbers so we have included our own page numbers, starting on the first page as page 1, and numbering the remaining pages consecutively.

Appellant further asserts that claim 21 "contains extensive peptide sequence information, over 96% of which is fixed" and "[t]he variability in the remainder of the sequences is distinctly described." *Id*. at 12–13. Therefore, according to Appellant, "[t]hese sequences are sufficient to satisfy any structural requirement and to provide context for the functional element of the claim" such that a "person of skill in the art would understand the subject matter being claimed and the scope of the claims." *Id.* at 13.

Appellant also contends that the Specification identifies the region of canine CD20 bound by three antibodies in Figure 2A and the method of determining the structure of an antibody bound to human CD20 is known as shown in Du.[3] *Id.* at 12. Therefore, according to Appellant, a person of skill in the art could determine the three-dimensional structure of cell surface expressed canine CD20 and the particular residues of the 1E4, 1G10, and 1G1 antibodies that form the canine CD20-binding paratope without undue experimentation. *Id.*

The Examiner responds that, although the Specification discloses certain regions of CD20 that are bound by the 1E4, 1G10 and 1G1 antibodies, "this assay only shows that certain amino acid residues of canine CD20 are required for binding of these antibodies" and "does not demonstrate that these are all or the only residues bound by the 1E4, 1G10 and 1G1 antibodies, and the skilled artisan cannot know from the teachings of the instant specification which, if any, additional residues of canine CD20 are bound by the disclosed antibodies." Final Act. 5.

[3] Du et al., Structural Basis for Recognition of CD20 by Therapeutic Antibody Rituximab, J. Biol. Chem., 15073–15080 (2007) ("Du").

The Examiner also finds that "[t]here is *no* apparent structural relationship between the antibody of the instant claims and the rituximab antibody of [Du]" and that the claimed antibodies bind canine CD20 while rituximab binds human CD20. Ans. 17. Furthermore, the Examiner contends, the 1E4, 1G10 and 1G1 antibodies do not tolerate the substitution of human CD20 sequences into their canine epitope as shown in Figures 2A–B. *Id.* Therefore, according to the Examiner, "[t]he skilled artisan cannot just apply the crystallization methods of [Du] to the crystallization of the 1G10 and 1G1 antibodies bound to canine CD20 in the absence of undue experimentation" because "these are unrelated antibodies binding structurally distinct antigens." *Id.*

We find that the Examiner's position is supported by a preponderance of the evidence. The Specification does not disclose 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. As found by the Examiner, the Specification does not disclose any members of the claimed genus because it does not disclose any 1G10 or 1G1 antibodies having any combination of variant amino acids that bind canine CD20 with an affinity of (Kd) at least 20 nM.

While the Federal Circuit has recognized that "the written description requirement can in some cases be satisfied by functional description," it has made clear that "such functional description can be sufficient only if there is also a structure-function relationship known to those of ordinary skill in the art." *In re Wallach*, 378 F.3d 1330, 1335 (Fed. Cir. 2004); *see also, Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002)

(holding that the written description requirement would be satisfied "if the functional characteristic of preferential binding . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed"); *Amgen Inc. v. Sanofi*, 782 F.3d 1367, 1378 (Fed. Cir. 2017) (holding that an "adequate written description must contain enough information about the actual makeup of the claimed products"). Here, Appellant provides a functional description of the claimed antibody — i.e., that it binds canine CD20 with an affinity (K_d) of at least 20 nM — but we do not find sufficient disclosure of a correlation between the claimed function and the structure of the antibodies that perform that function.

Appellant asserts that claim 21 "contains extensive peptide sequence information, over 96% of which is fixed" and "[t]he variability in the remainder of the sequences is distinctly described." Appeal Br. 12–13. However, we agree with the Examiner that the Specification's disclosure of a few 1E4 antibody mutants, each with only a single mutation, is not sufficient to demonstrate possession of the claimed genus of structurally dissimilar 1G1 and 1G10 antibody mutants, with multiple mutations, that bind canine CD20 with an affinity (K_d) of at least 20 nM. We, therefore, agree with the Examiner that the Specification does not disclose, and the skilled artisan cannot predict based on the disclosure in the Specification, which particular combinations of X_1 to X_6 light and heavy chain amino acids are sufficient to support the claimed binding to canine CD20.

Appellant's citation to *Ex parte Grosmaire* is inapposite because, in that case, the claims recited the CDR sequences, without any mutations, and the Specification described the CDR sequences that had to be present in order to meet the claimed binding limitation. *Grosmaire* at *5. In contrast,

the current claims include multiple potential amino acid substitutions in the light and heavy chain CDRs, and, as discussed above, the Specification does not include any examples of mutations within the 1G1 and 1G10 antibodies that result in antibodies that can bind to canine CD20 with an affinity (K_d) of at least 20 nM.

Appellant also argues that, even if the claimed mutations resulted in decreased affinity of antibody 1G10 by almost 100-fold, "those variants would still have an affinity greater than 20 nM and thus the variants would meet the functional limitation of the claim." However, Appellant has not provided any basis for this statement and, "[a]ttorneys' argument is no substitute for evidence." *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989).

We are also not persuaded by Appellant's argument that the Specification identifies the region of canine CD20 bound by three antibodies and the method of determining the structure of an antibody bound to human CD20 is known, so a person of skill in the art could generate epitope binding data for the claimed antibodies without undue experimentation. Appeal Br. 12. We agree with the Examiner that the Specification only shows that certain amino acid residues of canine CD20 are required for binding these unsubstituted antibodies but does not disclose which particular CDR residues of the 1G10 and 1G1 antibodies form the canine CD20-binding paratope. Furthermore, we also agree that information regarding rituximab's binding to human CD20 as disclosed in Du is not sufficient to provide one of ordinary skill in the art with an understanding of how mutants of different antibodies (1G10 and 1G1) might bind to a different antigen (canine CD20). Also, the fact that it might be obvious to determine which, if any, species of

antibody encompassed by the genus of claim 21 meets the claimed binding limitation does not demonstrate that Appellant possessed those antibodies. *See Ariad*, 598 F.3d at 1352 ("[A] description that merely renders the invention obvious does not satisfy the requirement.").

For the reasons described herein and those already of record, we sustain the Examiner's rejection of independent claim 21 under 35 U.S.C. § 112 as lacking sufficient written description. Claims 22–23 are not argued separately, and, therefore, fall with claim 21. *See* 37 C.F.R. § 41.37(c)(1)(iv).

CONCLUSION

For the reasons described herein and those already of record, we affirm the Examiner's rejection of claims 21–23.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
21–23	112, first paragraph	Written Description	21–23	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED