UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/790,247	07/02/2015	Tibor KELER	CDJ-367DV	1450

959 7590 06/10/2020

NELSON MULLINS RILEY & SCARBOROUGH LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER
DUFFY, BRADLEY

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
06/10/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte TIBOR KELER, HENRY C. MARSH, LIZHEN HE, LAURA A. VITALE, and LAWRENCE J. THOMAS

Appeal 2019-006094
Application 14/790,247
Technology Center 1600

Before JEFFREY N. FREDMAN, ELIZABETH A. LAVIER, and MICHAEL A. VALEK, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a method for inducing or enhancing an immune response using an antibody to CD27. The Examiner rejected claim 10 as failing to comply with the written description requirement. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

---

[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 Celldex Therapeutics, Inc. (*see* Appeal Br. 2).

[2] We reviewed and refer to the Specification of Aug. 7, 2015 ("Spec."); Final Action of Sept. 12, 2017 ("Final Act."); Appeal Brief of Oct. 9, 2018 ("Appeal Br."); and Examiner's Answer of Dec. 31, 2018 ("Ans."). A telephonic oral hearing was held on June 2, 2020.

Statement of the Case

Background

"Interactions between T cells and antigen-presenting cells involve a variety of accessory molecules that facilitate in the generation of an immune response. One such molecule is CD27, which binds CD70 and belongs to the tumor necrosis factor receptor (TNF-R) superfamily" (Spec. 1:11–14). "Agonistic monoclonal antibodies against CD27 have recently been shown to promote T cell responses and show promise as anti-cancer therapeutics" (*id.* at 1:30–31). "[T]here is a need in the art for further insight into the specific functional properties that make anti-CD27 antibodies therapeutically effective, as well as improved therapeutic antibodies against CD27 which are more effective for treating and/or preventing diseases" (*id.* at 2:2–5).

The Claim

Claim 10 is on appeal and reads as follows:

> 10. A method for inducing or enhancing an immune response against an antigen in a subject comprising administering to the subject a monoclonal antibody which binds to human CD27, in an amount effective to induce or enhance an immune response against an antigen, wherein the antibody comprises heavy and light chain variable region sequences having at least 95% identity to SEQ ID NOs: 37 and 43, respectively.

The Issue

The Examiner rejected claim 10 under 35 U.S.C. § 112(a) as failing to comply with the written description requirement (Ans. 3–7).

The Examiner finds that:

> With respect to antibodies that have sequences with 95% identity to SEQ ID NOs: 37 and 43, as evidenced below, the 6 antibody complementarity-determining regions (CDRs) are primarily responsible for the functions of an antibody, and the

> claimed antibodies include antibodies with multiple CDR modifications, including deletions, insertions and substitutions . . .
>
> The specification fails to adequately describe the genus, as a whole, because the skilled artisan could not immediately envision, recognize or distinguish as least most of its members from other antibodies, as the specification fails to describe its members as sharing any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of these variants.

(Ans. 5). The Examiner finds that "while the instant specification establishes that an antibody comprising the six CDRs of antibody mAb 1F5 binds CD27, the specification does not establish which residues in the CDRs are required for binding" (*id.* at 6). The Examiner finds "the disclosed species would not be considered representative of the claimed genus [i.e., antibodies comprising heavy and light chain variable region sequences having at least 95% identity to SEQ ID NOs: 37 and 43 that bind human CD27] as the CDR modifications encompassed by the claim is significantly broader and structurally distinct from the CDR modifications set forth in the species disclosed in the specification" (*id.* at 7).

Appellant contends the

> antibodies of claim 10 are defined in terms of a particular structure (*i.e.*, full-length heavy and light chain variable region sequences) and functional effect (*i.e.*, binding to human CD27 and inducing or enhancing an immune response against an antigen). Thus one of skill in the art could, indeed, readily distinguish members of the claimed genera of antibodies from other antibodies.

(Appeal Br. 3–4). Appellant identifies three species of antibodies where the "variable heavy chains of antibodies 1H8 and 3H12 share 93.3% and 97.5%

identity, respectively, with the variable heavy chain of antibody 1F5. Additionally, the variable light chains of antibodies 1H8 and 3H12 share 97.2'% and 100% identity, respectively, with the variable light chain of antibody 1F5" (*id.* at 4). Appellant contends the "three antibodies (i.e., 1F5, 1H8, and 3H12) possess common functional features. For example, all three antibodies (1) bind CD27 with similar affinities . . . (2) block binding of sCD70 . . . (3) compete for binding to CD27 . . . and (4) induce complement dependent cellular cytotoxicity (CDCC)" (*id.*).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that claim 10 fails to comply with the written description requirement?

Findings of Fact

1. The Specification teaches "[a]n 'antibody' refers, in one preferred embodiment, to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof" (Spec. 23:22–25). The Specification explains the "V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs" (Spec. 23:29–32). The Specification teaches "[a]ntibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs)" (Spec. 44:22–24) and that "antibody heavy and light chain CDR3

domains play a particularly important role in the binding specificity/affinity of an antibody for an antigen" (Spec. 48:1–3).

2. The Specification teaches:

> the invention provides anti-CD27 antibodies that induce or enhance effector cell function (e.g., cell killing via either ADCC and/or CDC). In one embodiment, the antibody induces at least about 30% specific lysis of CD27 expressing cells via ADCC at an antibody concentration of 10 μg/ml and/or induces at least about 30%CDC of CD27 expressing cells at a concentration of 10 μg/ml. Particular antibodies falling within this class exhibiting ADCC effector function include, *e.g.*, (*e.g.*, mAb comprising heavy and/or light chain variable region sequences comprising . . . SEQ ID NOs:37 and/or 43 (mAb 1F5).

(Spec. 4:21–29).

3. The Specification teaches that the antibodies encompass "conservative sequence modifications" (Spec. 9:27) as well as providing literal support for the 95% requirement[3] by teaching "[i]solated antibodies which include heavy and light chain variable regions having . . . at least 95% . . . or more sequence identity to any of the above sequences" (Spec. 10:15–18).

4. The Specification teaches that "[c]onservative amino acid substitutions include ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art" (Spec.

[3] We recognize that the Examiner's written description rejection is not based on new matter, but rather a failure to provide descriptive support for the full scope of the claim, so we cite this portion of the Specification simply to note that literal support for this limitation does exist.

31:14–17). The Specification explains that "[m]ethods of identifying nucleotide and amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art (see, *e.g.,* Brummell *et al., Biochem*. 32: 1180-1187 (1993); Kobayashi *et al. Protein Eng.* 12(10):879-884 (1999); and Burks *et al. Proc. Natl. Acad. Sci. USA* 94:412-417 (1997))" (*id.* at 25–28).

5. The Specification teaches the "comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm" (Spec. 32:10–12), and list a number of prior art algorithms to perform this analysis (*see* Spec. 32:13 to 33:3).

6. The Specification further teaches that:

> Methods for identifying residues that can be altered without removing antigen binding are well-known in the art (see, *e.g.,* Marks *et al.* (*Biotechnology* (1992) 10(7):779-83 (monoclonal antibodies diversification by shuffling light chain variable regions, then heavy chain variable regions with fixed CDR3 sequence changes), Jespers *et al*.(1994) *Biotechnology* 12(9):899-903 (selection of human antibodies from phage display repertoires to a single epitope of an antigen), Sharon *et al.* (1986) *PNAS USA* 83(8):2628-31 (site-directed mutagenesis of an invariant amino acid residue at the variable-diversity segments junction of an antibody); Casson *et al.* (1995) *J. Immunol.* 155(12):5647-54 (evolution of loss and change of specificity resulting from random mutagenesis of an antibody heavy chain variable region).

(Spec 48:30 to 49:6).

7. The Specification also teaches that "in another embodiment, mutations can be introduced randomly along all or part of an anti-CD27 antibody coding sequence, such as by saturation mutagenesis, and the

resulting modified anti-CD27 antibodies can be screened for binding activity" (Spec. 31:29–32).

8. Figure 15 of the Specification is reproduced in part below:

```
                          1                                                  50
1F5-1H5 V-H         (1)  MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSS
1H8-B4 V-H          (1)  MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFNI
3H12-1E12 V-H       (1)  MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCATSGFTFSS

                          51                                                 100
1F5-1H5 V-H        (51)  YDMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYL
1H8-B4 V-H         (51)  YDMHWVRQAPGKGLEWVAVIWYDGSNQYYADSVKGRFTISRDNSKNTLYL
3H12-1E12 V-H      (51)  YDMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYL

                         101                                                143
1F5-1H5 V-H        (101)  QMNSLRAEDTAVYYCARGSGN-----WGFFDYWGQGTLVTVSS
1H8-B4 V-H         (101)  QMNILRAEDTAVYYCARG-TH-----WGYFDYWGQGTLVTVS$
3H12-1E12 V-H      (101)  QMNSLGDEDTAVYYCARGSGN-----WGFFDYWGQGTLVTVSS
```

This portion of Figure 15 of the Specification shows alignment of the heavy chain of antibodies 1H8 and 3H12 with 1F5. Appellant asserts, and the Examiner acknowledges, that the 1H8 and 3H12 sequences share 97.2% and 100% identity with the 1F5 sequence, respectively (*see* Final Act. 7–8). The Examiner further acknowledges that the light chain sequences of 1H8 and 3H12 share 93.3% and 97.5% identity respectively with 1F5 (*see* Final Act. 8; *cf.* Figure 16 of Specification).

9. Table 1 of the Specification is reproduced in part below:

Table 1

Characterization of selected anti-CD27 mAb

mAb	Half-max binding to human CD27(M)**	Half-max binding to human CD27(μg/ml)**	Half-max binding to monkey CD27(μg/ml)**
1H8	4.3E-10	0.064	0.105
3H12	5.7E-10	0.085	0.123
1F5	3.9E-10	0.059	0.12

Table 1 shows that antibodies 1F5, 1H8, and 3H12 bind CD27 with half max values of 0.059 µg/ml, 0.064 µg/ml, and 0.085 µg/ml respectively (see Spec. 75:10–20).

10. The Specification teaches that "several of the antibodies (including 1F5, 1H8, 3H12 and 1A4) had the property of blocking or at least significantly inhibiting the binding of sCD70" (Spec. 76:11–12).

11. The Specification teaches "a first set of the human mAbs (comprising mAbs 1F5, 1H8 and 3H12) cross-competed with each other" for binding to CD27 (Spec. 77:15–16).

12. Figure 11 of the Specification is reproduced below:

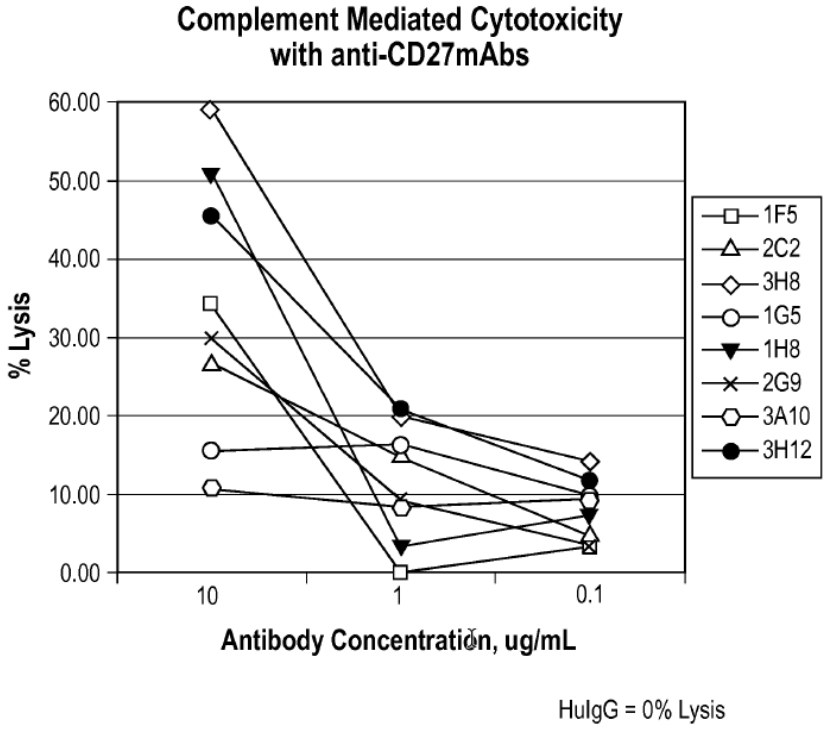

Fig. 11

Figure 11 shows that "a number of the anti-CD27 antibodies displayed significant CDCC activity," including 1F5, 3H8 and 3H12 (Spec. 78:3–4).

Principles of Law

> An adequate written description must contain enough information about the actual makeup of the claimed products — "a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials," which may be present in "functional" terminology "when the art has established a correlation between structure and function."

Amgen, Inc. v. Sanofi, 872 F.3d 1367, 1378 (Fed. Cir. 2017) (*citing Ariad Pharm., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc)).

The Federal Circuit has found that "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 1351 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568–69 (Fed. Cir. 1997)).

Analysis

In analyzing claim 10 in view of the Specification, we appreciate "the purpose of the written description requirement is to 'ensure 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 of art as described in the patent specification.'" *Ariad*, 598 F.3d at 1353 (*citing Univ. of Rochester v. G.D. Searle & Co., Inc*., 358 F.3d 916, 920 (Fed. Cir. 2004)).

Claim 10 sets forth a method in which a monoclonal antibody composed of a heavy and light chain sequences with at least 95% identity to SEQ ID Nos: 37 and 43, respectively, that binds to CD27 and functions to induce or enhance immune response to an antigen.

The Specification teaches that the inventor's contribution encompasses particular antibody sequences that function to bind CD27 (FF 2). The Specification teaches that the essential binding regions in antibodies, termed CDR sequences, were known (FF 1). The Specification teaches that some conservative amino acids may be substituted in the claimed amino acid sequences without eliminating function, and that it was well known how to identify such conservative changes (FF 4, 6). Claim 10 limits the number of conservative substitutions permitted by requiring 95% identity (*cf*. FF 3, 5), a value which permits no more than about seven substitutions in the heavy chain sequence and no more than about six substitutions in the light chain sequence (*see* FF 8). Lastly, the Specification teaches three different species of V_H and V_L sequences that function to bind CD27 (FF 8).

We find that claim 10 recites a sufficiently precise definition and structural formula that would allow the ordinary artisan to identify anti-CD27 antibodies that fall within the scope of claim 10 from those antibodies that do not fall within the scope of claim 10. That is, claim 10 does "particularly point out and distinctly circumscribe the outer boundaries of a claimed invention," *AbbVie Deutschland Gmbh & Co., KG v. Jassen Biotech, Inc.* , 759 F.3d 1285, 1300 (Fed. Cir. 2014). Claim 10 establishes this boundary both by providing specific amino acid sequences of SEQ ID Nos: 37 and 43 and by requiring other antibodies to retain 95% identity with

those amino acid sequences. In addition, claim 10 requires a functional activity of antibodies of binding to CD27 that serves to further delimit the genus of antibodies encompassed by claim 10.

Abbvie further explains that to satisfy the written description requirement, "merely drawing a fence around a perceived genus is not a description of the genus. One needs to show that one has truly invented the genus, *i.e*., that one has conceived and described sufficient representative species encompassing the breadth of the genus." *Id*. The instant Specification provides three representative species, 1H8, 3H12, and 1F5 (FF 8–12). The Specification further demonstrates that these species exhibit both the structure recited in claim 10 (i.e., comprises heavy and light chain variable region sequences having at least 95% identity to SEQ ID NOs: 37 and 43) as well as the recited function (i.e., they bind to human CD27 and induce/enhance an immune response) (FF 8–12). Thus, Appellant's description correlates the structure of these species to the claimed function. The Specification also provides a detailed explanation of methods that allow the generation of other functional species that also fall within the scope of claim 10 (FF 4, 6).

We recognize that the Examiner asserts "one of skill in the art would not consider any of the disclosed species as representative of the disclosed genus of antibodies that bind CD27 which can have 5 positions deleted, inserted or substituted or any combination thereof in a single CDR" (Ans. 7). We also recognize that the Examiner has cited references regarding

unpredictability, and specifically cites Winkler[4] as teaching that "a single amino acid change in a CDR can result in unpredictable and substantial changes in antibody specificity" (Ans. 6).

However, we are not persuaded that an exemplary species with, essentially, a novel CDR is necessary to establish a reasonable number of species for written description purposes. Instead, we agree with Appellant that as of

> the relevant priority date, it was well within the ordinary skill in the art to identify and test amino acid residues within the CDR domains of a given antibody that are amenable to amino acid substitution and still retain the claimed functions (i.e., binding to human CD27 and the ability to induce or enhance an immune response).

(Appeal Br. 5). "[T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue." *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

In *Invitrogen Corp. v. Clontech Laboratories, Inc*., 429 F.3d 1052, 1073 (Fed. Cir. 2005), there was evidence "that the sequences for these and other representative [species] were known" and that the opposing party had "not adduced contrary evidence establishing a genuine issue of fact." *Id.* We note that the Examiner here also does not provide evidence that, as of the instant filing date, an ordinary artisan in the field of antibody technology, would have found insufficient description in the Specification of an antibody

---

[4] Winkler et al., *Changing the Antigen Binding Specificity by Single Point Mutations of an Anti-p24 (HIV-1) Antibody*, 165 J. Immunology 4505–14 (2000).

that comprises heavy and light chain variable region sequences having at least 95% identity to SEQ ID NOs: 37 and 43 and binds human CD27 in an amount effective to induce or enhance an immune response. To the extent that there would be some unpredictability in any particular altered antibody sequence,

> it is almost always possible to so construe a claim as to have it read on inoperative embodiments. . . . , but the alternative of requiring an applicant to be so specific in his claims "as to exclude materials known to be inoperative and [which] even those not skilled in the art would not try" would result in claims which would fail to comply with 35 U.S.C. § 112, second paragraph, because they would be so detailed as to obscure, rather than to particularly point out and distinctly claim, the invention.

In re Smythe, 480 F.2d 1376, 1385 (CCPA 1973). In this case, while claim 10 excluding inoperative embodiments might not be indefinite, it would be narrower than the scope supported by the disclosure in the Specification. Thus, Appellant has demonstrated descriptive support for the embodiments encompassed by claim 10.

Conclusion of Law

A preponderance of the evidence of record does not support the Examiner's conclusion that claim 10 fails to comply with the written description requirement.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
10	112(a)	Written Description		10
Overall Outcome				10

REVERSED