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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOHN SIMARD

Appeal 2019-003759
Application 15/584,360
Technology Center 1600

Before ERIC B. GRIMES, RICHARD M. LEBOVITZ, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

The claims in this appeal are directed to a purified antibody. The Examiner rejected the claims under 35 U.S.C. §§ 101 and 102. Pursuant to 35 U.S.C. § 134, Appellant[1] appeals the Examiner's determination that the claims are unpatentable. We have jurisdiction for the appeal under 35 U.S.C. § 6(b).

We AFFIRM.

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[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 XBiotech, Inc. Br. 3 (entered May 9, 2018).

STATEMENT OF THE CASE

Claims 1 and 3, the only pending claims in the application, stand finally rejected by the Examiner as follows:

Claims 1 and 3 under pre-AIA 35 U.S.C. § 102(b) as anticipated by Glanville et al., *Proc. Nat'l. Acad. Sci.*, 2009, 106(48):20216–20221 ("Glanville"). Ans. 3.

Claims 1 and 3 under 35 U.S.C. § 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

Claim 1, the only independent claim on appeal, is reproduced below:

> 1. A purified antibody comprising
> a variable region amino acid sequence that promotes binding of the immunoglobulin to a target antigen,
> wherein the variable region amino acid sequence is determined by screening a phage display library comprising variable region encoding nucleic acid sequences isolated by PCR amplification of a cDNA library made from B lymphocytes using human immunoglobulin variable region leader-specific primers,
> wherein the human subject was previously determined to possess antibodies specific for the target antigen and
> the variable region amino acid sequence has somatic hypermutations in its first N-terminal 8 amino acids.

REJECTION BASED ON GRANVILLE

Claim 1 requires an antibody comprising a variable region with somatic hypermutations in the first N-terminal 8 amino acids of the variable region.

The Examiner found that Glanville describes a phage library encoding human variable heavy and variable light chains. Ans. 3. The Examiner

found that the library was derived from peripheral blood and splenic human lymphocytes comprising B cells. *Id.* The Examiner found that the "variable regions comprise the somatic hypermutations from the sequences they were derived from by PCR (page 20216, first column), and include such hypermutations in the heavy chain CDRs (e.g. see Fig 2 and ¶ linking first and second columns, page 20219), considered to be 'the first 8 amino acids of the variable region'" recited in claim 1. Ans. 3–4. The Examiner made this conclusion for the following reasons:

> This is because such a [variable] region is not precisely defined in the specification, and the CDRs themselves are considered variable regions or variable domains by Glanville et al. Further, it is noted no such library has been prepared and characterized in the specification, thus, the specification provides no means for comparison as to the scope of the term "the first 8 amino acids of the variable region".

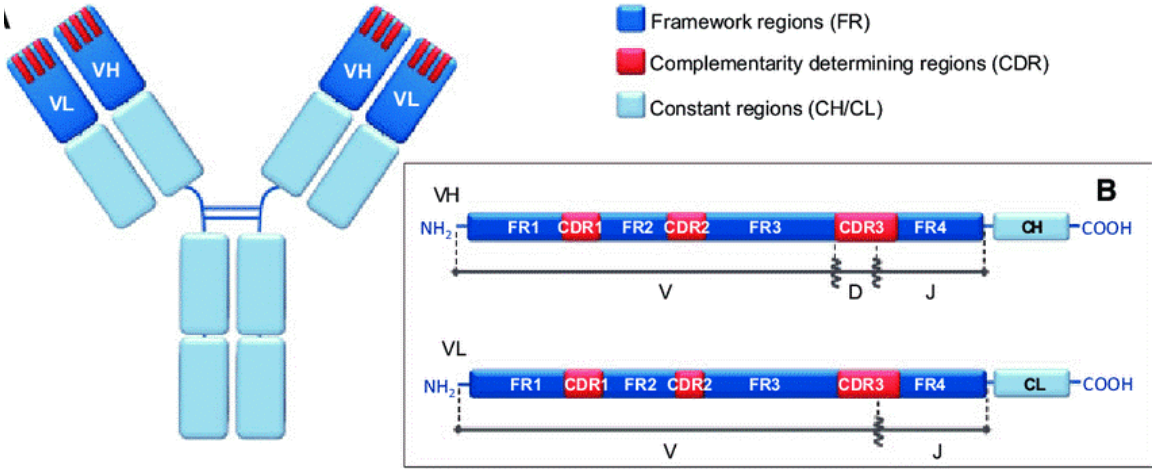
Ans. 4.

The issue in this rejection is whether the claimed "variable region amino acid sequence" having "somatic hypermutations in its first N-terminal 8 amino acids" is within the CDR regions described by Granville. To address this question, we must begin with claim interpretation.

Claim interpretation

During patent examination proceedings, claim terms are given "the broadest reasonable meaning . . . in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

The claimed antibody comprises "a variable region amino acid sequence that promotes binding of the immunoglobulin to a target antigen." A naturally-occurring antibody has a variable region which is the part of the antibody that binds to the antigen. The figure reproduced below shows the antibody structure.[2]



As shown in the figure reproduced above, the antibody has variable regions VL and VH (dark blue) and constant regions CH and CL (aqua). The variable region of each heavy and light chain has four framework regions ("FR") depicted as blue bars and three complementarity determining regions ("CDR") depicted as the red bars. The inset to the figure shows that framework region FR1 is at the amino-most terminus of each variable light and heavy chain.

Diversity in each chain is determined by "somatic hypermutation of variable domain nucleotides, with a concentration on CDR encoding

[2] The figure is reproduced from Mirsky et al., 2014, *Mol. Biol. Evol.*, 32(3):806–819. The publication is provided herein and listed on the attached PTO-892. Mirsky provides the figure as general background and is cited as evidence of what was known prior to the date of the invention.

regions." Glanville 20216 (col. 1). "As expected, most of hypermutations accumulate in the complementarity determining regions (CDRs; see fig. 1 [same figure reproduced above]), which are directly involved in binding to the antigen. This is partially due to the higher presence of mutational hot-spot sequences in these regions . . . , and partially due to their plasticity." Mirsky 807 (col. 2). "CDRs constitute structurally flexible loops, and therefore can accept a wider range of mutations compared with framework regions (FRs), which have mainly a scaffolding role and must keep an ordered-barrel structure." *Id.* "The three CDR regions on each V-region heavy and light chain show the most sequence diversity. Because of this diversity, these regions are also called hypervariable regions." Spec. ¶ 17. The three CDR regions are shown in Mirsky's figure reproduced above.

"variable region amino acid sequence has somatic hypermutations in its first N-terminal 8 amino acids"

The Specification explains that PCR is used to make libraries of plasmids, where PCR primers are used to amplify "cDNAs encoding heavy and light Ig chain variable regions (V-regions) from peripheral blood leukocytes (PBLs)." Spec. ¶ 9. The Specification teaches that "[i]n the phage display approach, human Ig V-region genes are cloned into bacteriophage in order to display Ab fragments on the surfaces of bacteriophage particles." *Id.* The Specification teaches that the generation of low affinity antibodies is a major limitation of the phage display system. Spec. ¶¶ 10, 11. The Specification states that a reason why phage display commonly generates low affinity antibodies is that V-region primers based on the germline sequences have been used, which "amplify the Ig sequences

from *inside* the antibody V-regions" and thus "the repertoire will be completely devoid of antibodies with hypermutation in the 5' end of the V-region." Spec. ¶ 12. The Specification states that the invention stems, *inter alia*, from finding that "two amino acid substitutions in the sections of V-regions *outside the CDRs* had a significant effect on an Ab's affinity for Ag" which led to the "startling realization that the conventional method of amplifying V-region sequences using primers for 5' germline end sequences resulted in libraries that were missing many of those V-regions that have mutations at their 5' end." Spec. ¶ 19 (emphasis added).

Furthermore, the Specification discloses:

> Importantly, it was also realized that it was those missing V-regions that would be expected to be included in the highest affinity Abs. The *first ten amino acids in a V-region can and often do contain somatic hypermutations*. A single amino acid change in this region can affect antibody binding.

Spec. ¶ 19 (emphasis added).

The Specification further explains:

> In the innovative approach described herein, rather than amplifying V-regions using PCR primers for 5' V-region sequences, V-regions are amplified using leader sequence-specific forward primers. Because the leader sequence is just upstream of the V-region genes, all V-region sequences, including those with 5' end mutations, are amplified. The resulting library therefore contains a more complete V-region repertoire than those prepared by the conventional method (which results in the loss of all V-region sequences that are somatically hypermutated).

Spec. ¶ 20.

Based on the disclosure in the Specification and the knowledge available at the time of the invention about antibody structure, we understand "the sections of V-regions outside the CDRs" described in the

Specification at paragraph 19 to be the framework region FR1 shown in the antibody depicted in the figure reproduced above. The "first ten amino acids" in the V-region described in paragraph 19 are the "missing V-regions." These amino acids are "outside the CDRs" and therefore fall within framework region FR1 because this region is described as the region missing when using conventional methods (Spec. ¶ 19 as reproduced above). This framework region is obtained by using the leader-specific primers that are recited in the claim ("cDNA library made from B lymphocytes using human immunoglobulin variable region leader-specific primers"). Spec. ¶ 20 (reproduced above).

The claim recites that the "variable region amino acid sequence has somatic hypermutations in its first N-terminal 8 amino acids." Since FR1 is at the N-terminus of the antibody chain, and the first ten amino acids of the V region are outside the CDR region, we interpret the recited eight amino acids to be *outside the CDR regions*, and *in the framework region*.

Product-by-process claim

Claim 1 is a "product-by-process" claim because the product – the antibody – is claimed as a product of a process of "screening a phage display library comprising variable region encoding nucleic acid sequences isolated by PCR amplification of a cDNA library made from B lymphocytes using human immunoglobulin variable region leader-specific primers." A product-by-process limitation defines a product in terms of how it is made. *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1315 (Fed. Cir. 2006). "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself."

In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985). The claimed structural requirement that "the variable region amino acid sequence has somatic hypermutations in its first N-terminal 8 amino acids" is imparted to the claimed antibody by the process by which it is made, namely, by using leader-specific primers to amplify the N-terminal framework region.

Discussion

The Examiner found that Granville describes antibodies with somatic hypermutations in the CDR regions. Ans. 3–4. The Examiner did not find that Granville describes antibodies with somatic hypermutations in the framework region. As explained in the claim interpretation section, the Specification expressly distinguished hypermutations in the CDR region from those hypermutations outside the CDR region in the "first ten amino acids in a V-region." Spec. ¶¶ 19, 20. It would be unreasonable in light of the Specification to interpret the first N-terminal 8 amino acids to reside in a CDR region. Consequently, we conclude that Examiner erred in finding that the claimed "variable region amino acid sequence has somatic hypermutations in its first N-terminal 8 amino acids" is a CDR region. The anticipation rejection of claims 1 and 3 based on Glanville is reversed.

REJECTION BASED ON § 101

The Examiner finally rejected claims 1 and 3 under 35 U.S.C. § 101 because the claimed invention is directed to a judicial exception to patent eligibility. Final Act. 3; Ans. 3.

Principles of Law

Under 35 U.S.C. § 101, an invention is patent-eligible if it claims a "new and useful process, machine, manufacture, or composition of matter." However, not every discovery is eligible for patent protection. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Id.* The Supreme Court articulated a two-step analysis to determine whether a claim falls within an excluded category of invention. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014); *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 75–77 (2012).

In the first step, it is determined "whether the claims at issue are directed to one of those patent-ineligible concepts." *Alice*, 573 U.S. at 217. If it is determined that the claims are directed to an ineligible concept, then the second step of the two-part analysis is applied in which it is asked "[w]hat else is there in the claims before us?" *Id.* (alteration in original). The Court explained that this step involves

> a search for an 'inventive concept' — *i.e.*, an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'

Alice, 573 U.S. at 217–18 (citing from *Mayo*, 566 U.S. at 75–77) (alteration in original).

Alice, relying on the analysis in *Mayo* of a claim directed to a law of nature, stated that in the second part of the analysis, "the elements of each claim both individually and 'as an ordered combination'" must be considered "to determine whether the additional elements 'transform the

nature of the claim' into a patent-eligible application." *Alice*, 573 U.S. at 217.

The USPTO has published revised guidance on the application of 35 U.S.C. § 101. USPTO's January 7, 2019 Memorandum, *2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50, 51–57 (2019) ("2019 Eligibility Guidance"). This guidance provides additional direction on how to implement the two-part analysis of *Mayo* and *Alice*.

Step 2A, Prong One, of the 2019 Guidelines, looks at the specific limitations in the claim to determine whether the claim recites a judicial exception to patent eligibility. In Step 2A, Prong Two, the claims are examined to identify whether there are additional elements in the claims that integrate the exception in a practical application, namely, is there a "meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception." 84 Fed. Reg. 54 (2. Prong Two).

If the claim recites a judicial exception that is not integrated into a practical application, then as in the *Mayo/Alice* framework, Step 2B of the 2019 Guidelines instructs us to determine whether there is a claimed inventive concept to ensure that the claims define an invention that is significantly more than the ineligible concept, itself. 84 Fed. Reg. 56. In making this determination, we must consider whether there are specific limitations or elements recited in the claim "that are not well-understood, routine, conventional activity in the field, which is indicative that an inventive concept may be present" or whether the claim "simply appends well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception,

indicative that an inventive concept may not be present." 84 Fed. Reg. 56 (footnote omitted).

With these guiding principles in mind, we proceed to determine whether the claimed subject matter in this appeal is eligible for patent protection under 35 U.S.C. § 101. As explained in more detail below, we conclude that the claims are directed to patent-ineligible subject matter.

Discussion

Step 2A, Prong One

In Step 2A, Prong One, of the 2019 Guidelines, the specific limitations in the claim are examined to determine whether the claim recites a judicial exception to patent eligibility, namely whether the claim recites an abstract idea, law of nature, or natural phenomenon.

The Examiner found that claims 1 and 3 are directed to human antibodies which do not differ from the same antibodies found in nature and therefore constitute a work of nature and a natural law or phenomenon. Ans. 4. The Examiner found that the claims do not "include additional elements that are sufficient to amount to significantly more than the judicial exception because the recited antibodies are no different in their biological properties than those found in the organism from which they were derived, i.e. the recited antibodies are derived from human sequences and comprise somatic mutations found in nature." *Id.*

We agree with the Examiner's determination.

The 2019 Guidelines do not change existing guidelines in how it is determined whether a claim recites a law of nature or natural phenomenon. 84 Fed. Reg. 54, footnote 20.

The claimed antibody comprises "a variable region amino acid sequence that promotes binding of the immunoglobulin to a target antigen." The variable region therefore has its natural function in binding antigen. The variable sequences which make up the antibody are identified from a cDNA library made from B lymphocytes from "the human subject . . . previously determined to possess antibodies specific for the target antigen." The sequences are therefore naturally occurring because they are derived from a human subject. There are no other limitations in the claim that we have been directed to that would distinguish the antibody from one found in nature.

Appellant contends that the rejection is incorrect because the claims "recite a purified antibody which is a composition of matter, and 35 U.S.C. § 101 expressly indicates that compositions of matter are statutory subject matter." Br. 8. Appellants also states that "the plain language of section 101 does not mention anything about a law of nature, a natural phenomenon, or an abstract idea, and the Office has not cited any other authority (case law) from which the alleged 'judicial exception' to 35 U.S.C. 101 is derived." *Id.*

Appellant's argument is unavailing. It is true that 35 U.S.C. § 101 states that a "composition of matter" is patentable subject matter if the conditions of the Patent Act are met. However, the Supreme Court expressly held that there are exceptions to 35 U.S.C. § 101: "Laws of nature, natural phenomena, and abstract ideas are not patentable." *Ass'n for Molecular Pathology v. Myriad Genetic, Inc.*, 569 U.S. 576, 589 (2013).

> Rather, "'they are the basic tools of scientific and technological work'" that lie beyond the domain of patent protection. . . . As the Court has explained, without this exception, there would be considerable danger that the grant of patents would "tie up" the

> use of such tools and thereby "inhibit future innovation premised upon them." . . . This would be at odds with the very point of patents, which exist to promote creation. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (Products of nature are not created, and "'manifestations ... of nature [are] free to all men and reserved exclusively to none'").

Id.

The claims in *Myriad* included "composition claims," such as a claim to "[a]n isolated DNA coding for a BRCA1 polypeptide.'" *Myriad*, 569 U.S. at 584 (alteration in original). Reading the DNA claim as being directed to an isolated BRCA1 gene, the Court recognized that Myriad had "found an important and useful gene," but concluded that "separating that gene from its surrounding genetic material is not an act of invention." *Id.* at 591. The Court found that Myriad's claim "fell squarely within the law of nature exception." *Id.* "Myriad found the location of the BRCA1 and BRCA2 genes, but that discovery, by itself, does not render the BRCA genes 'new . . . composition[s] of matter,' § 101, that are patent eligible." *Id.* Thus, Appellant's argument that a composition of matter is statutory and cannot be rejected under § 101 is not a correct interpretation of the law.

Step 2A, Prong Two

Prong Two of Step 2A under the 2019 Guidance asks whether there are additional elements that integrate the exception into a practical application. As in the *Mayo*/*Alice* framework, we must look at the claim elements individually and "as an ordered combination" to determine whether the additional elements integrate the recited law of nature into a practical application.

The claims are directed to a product of nature, an antibody that has

been purified. Under *Myriad*, the claim falls within a law of nature exception. Appellant did not identify additional elements in the claim, which would integrate the law of nature into a practical application. We find none, as well, because the process steps in the claim do not distinguish the claimed antibody from one found in nature.

Step 2B

If the judicial exception is not integrated into a practical application, then Step 2B of the 2019 Guidelines, as in the *Mayo/Alice* framework, asks whether there is an inventive concept. To determine whether an unpatentable law of nature has been transformed "into a patent-eligible application of such law," the Court in *Mayo* held that the claim as a whole must be examined to determine whether it "also contain[s] other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *See Mayo*, 566 U.S. at 72–73.

Appellant did not identify an inventive concept in the claim that would ensure that the claim is significantly more than a patent on the natural law. Even if the step of using a leader primer is not described in the prior art, the claim is to the product of nature, a patent-ineligible composition, and not the method of making it.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 3	102(b)	Glanville		1, 3
1, 3	101	Eligibility	1, 3	
Overall Outcome			1, 3	

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