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EPA - BOZICEVIC FIELD & FRANCIS LLP
BOZICEVIC, FIELD & FRANCIS
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

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ALLEN, MICHAEL D

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte FERNANDO JOSE REBELO DO COUTO, KRISTIN BETH HENDRICKS, STACEY ELLEN WALLACE, and GUO-LIANG YU

_____

Appeal 2018-001243
Application 14/518,977
Technology Center 1600

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Before RICHARD M. LEBOVITZ, JEFFREY N. FREDMAN, and TAWEN CHANG, *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 of screening for an antibody. The Examiner rejected the claims as indefinite, as of improper dependent form, as directed to non-statutory subject matter, and as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] Appellants identify the Real Party in Interest as Abcam plc. (*see* App. Br. 3).

[2] We have considered and herein refer to the Specification of Oct. 20, 2014 ("Spec."); Final Office Action of Dec. 28, 2016 ("Final Action"); Appeal Brief of May 25, 2017 ("App. Br."); Examiner's Answer of Oct. 4, 2017 ("Ans."); and Reply Brief of Nov. 17, 2017 ("Reply Br.").

Statement of the Case

Background

"Because of their ability to target virtually any molecule with exquisite specificity, monoclonal antibodies have the potential to become one of the main therapeutic agents of the future" (Spec. 1:10–12). "[H]owever the first attempts to fulfill the potential were disappointing because monoclonal antibodies used in therapy elicit a strong immune response in patients" (*id.* at 1:12–14). "In order to decrease these responses, efforts have been made to replace as much as possible of the non-human sequence of an antibody with human sequences using recombinant DNA technology" (*id.* at 1:27–29). "[M]any humanized antibodies are still highly immunogenic to a large proportion of patients. This is thought to be because the CDRs themselves are immunogenic" (*id.* at 2:15–17).

"[T]here is a need for humanization methods that reduce the immunogenicity of CDR regions of a non-human antibody in humans" (*id.* at 2:27–29).

The Claims

Claims 37, 39–43, 45–49, and 52 are on appeal. Claim 37 is sole independent claim, is representative and reads as follows:

> 37. A method of screening for an antibody, the method comprising:
>
> (a) immunizing an animal with an antigen;
>
> (b) obtaining the amino acid sequence of a plurality of antibodies from the immunized animal that bind to the antigen:
>
> (c) identifying a plurality of substitutable positions in the antibodies by: (i) aligning the amino acid sequences: (ii) grouping the antibodies according to their sequence similarity to produce groups of related antibodies and (iii) identifying positions at which the amino acid varies;

> (d) making a library of candidate antibodies, wherein the variant antibodies comprise amino acid substitutions at the substitutable positions; and
>
> (e) screening the variant antibodies to identity an antibody having a desirable activity.

The Rejections

A. The Examiner rejected claims 45 and 49 under 35 U.S.C. § 112(b) as indefinite (Ans. 2).

B. The Examiner rejected claim 45 under 35 U.S.C. § 112(d) as being of improper dependent form (Ans. 2–3).

C. The Examiner rejected claims 37, 39–43, 45–49, and 52 under 35 U.S.C. § 101 as directed to non-statutory subject matter (Ans. 3–4).

D. The Examiner rejected claims 37, 39–43, 45–49, and 52 under 35 U.S.C. § 103(a) as obvious over Rader,[3] Moe,[4] Watkins,[5] and Wu[6] (Ans. 4–8).

A. 35 U.S.C. § 112(b), indefiniteness

The Examiner finds "[c]laim 45 recites 'directed amino acid substitutions'. It is not clear what directed means in this phrase. There is no special definition in the specification thereof. Therefore, the metes and bounds of this claim are indefinite" (Ans. 2). The Examiner finds "[c]laim

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[3] Rader et al., *The Rabbit Antibody Repertoire as a Novel Source for the Generation of Therapeutic Human Antibodies*, 275 (18) J. BIOL. CHEM. 13668–76 (2000).
[4] Moe et al., US 2010/0260762 A1, published Oct. 14, 2010.
[5] Watkins et al., US 2003/0099655 A1, published May 29, 2003.
[6] Wu et al., *Stepwise in vitro affinity maturation of Vitaxin, an $\alpha_v\beta_3$-specific humanized mAb*, 95 PROC. NATL ACAD. SCI. USA 6037–42 (1998).

49 recites increased affinity but does not recite the comparison to be made to get the increase and so this claim is indefinite" (Ans. 2).

Appellants contend "a person of ordinary skill in the art in light of the present application would understand that a directed amino acid substitution is 'a substitution that make the amino acid sequence of an antibody more similar to that of a related antibody'. Specification at page 12, lines 22-23" (App. Br. 4). Appellants also contend regarding claim 49 that the "comparison is made with the affinity of the related antibodies" (App. Br. 4).

We agree with Appellants. As to claim 45, the Specification identifies four different types of substitutions: humanizing, directed, random, and conservative (*see* Spec. 12:20–25) and as noted by Appellants, explains that a directed substitution is "e.g., a substitution that makes the amino acid sequence of an antibody more similar to that of a related antibody" (Spec. 12:22–23). The Specification also provides a more detailed discussion of directed substitutions (*see* Spec. 20:13–21:4). We are not persuaded by the Examiner's argument that "the full breadth of the phrase is not defined by the Specification" (Ans. 19). That claim 45 broadly encompasses any substitutions that make an antibody more like some other antibody does not render the claim indefinite, only broad. Even "undue breadth is not indefiniteness." *In re Johnson*, 558 F.2d 1008, 1016 n.17 (CCPA 1977).

As to claim 49, the claim expressly recites that the comparison is the affinity of the desirable antibodies to a particular antigen relative to other antibodies. Again, claim 49 may be broad because the comparison may be to any antibody that is related in any way, but as already noted, "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693, 169 USPQ 597, 600 (CCPA 1971).

B. 35 U.S.C. § 112(d), improper dependent form

The Examiner finds that "[c]laim 45 recites directed substitutions. However, there appears to be no difference between this phrase and the substitutions of claim 37 on which claim 45 depends. Therefore, claim 45 does not further limit" (Ans. 3).

Appellants contend "directed amino acid substitution is a substitution that makes the amino acid sequence of an antibody more similar to that of a related antibody. As such, claim 45 further limits claim 37 on which claim 45 depends" (App. Br. 5).

We agree with Appellants. As already noted, claim 37 encompasses at least four different types of substitutions including humanizing, directed, random, and conservative (*see* Spec. 12:20–25) and claim 45 limits the method to a particular one of these types, those that are "directed amino acid substitutions." We are not persuaded by the Examiner's argument that "whether the mutation is humanizing or making one antibody structurally similar to a related antibody, for example, all would be considered directed" (Ans. 21) because, at a minimum, directed substitutions limits claim 37 to further exclude random substitutions, an alternative expressly discussed in the Specification (*see* Spec. 12:23–24).

C. 35 U.S.C. § 101

The Examiner finds the claims

> are directed to an abstract idea. This idea can be found in claim 37c. Identifying substitutable positions via comparison of at least two protein sequences through sequence alignment and identification of varying residues is an abstract idea. Addition of the step of grouping antibody sequences also adds to this abstract idea. Furthermore, this abstract idea also

> contains a natural phenomenon/law of nature. This is the correlation between sequence variation and substitutable positions. Thus, the claims are clearly drawn to judicial exceptions.

(Ans. 3). The Examiner further finds the "ordered combination of the active steps of the instant claims is well-understood, routine and conventional. It is routine in the art to immunize and animal to generate antibodies against the immunogen/target antigen. It is routine to sequence the resulting antibodies and to compare their sequences for differences" (Ans. 4).

Appellants contend that "claims are not directed to an abstract idea because the claimed method for screening antibodies is implemented using a set of limited rules specifically designed to improve existing technology for identifying antibodies that have an improved activity" (App. Br. 7). Appellants contend that

> consistent with the court's decision in *Rapid Litigation Management v. CellzDirect*, the end result of the claimed method is not simply an observation or detection of variant antibodies, but instead, the claims recite a number of steps that obtain and identify variant antibodies to achieve a desired outcome (generating a library of antibodies and identifying a novel antibody having a desirable activity).

(App. Br. 10). Appellants contend "the claims recite patent eligible subject matter because the claims yield significantly more than the judicial exception" (App. Br. 11).

The Alice Test

The Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit exceptions: "[l]aws of nature, natural phenomena, and abstract ideas" are not patentable. *See, e.g.*, *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014).

In determining whether a claim falls within an excluded category, we are guided by the Supreme Court's two-step framework, described in *Mayo* and *Alice*. *Id.* at 217–18 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 75–77 (2012)). In accordance with that framework, we first determine if there is a judicial exception. *See Alice*, 573 U.S. at 219 ("On their face, the claims before us are drawn to the concept of intermediated settlement, *i.e.*, the use of a third party to mitigate settlement risk.") Although method claims are generally eligible subject matter, claims that are directed only to abstract ideas, laws of nature, and/or natural phenomena are directed to patent ineligible concepts. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015).

If the claim recites an abstract idea, we turn to the second step of the *Alice* and *Mayo* framework, where "we must examine the elements of the claim to determine whether it contains an 'inventive concept' sufficient to 'transform' the claimed abstract idea into a patent-eligible application." *Alice*, 573 U.S. at 221 (quotation marks omitted).

2019 Guidance

The United States Patent and Trademark Office published revised guidance on the application of 35 U.S.C. § 101. USPTO's *2019 Revised Patent Subject Matter Eligibility Guidance* ("Guidance").[7] Under the Guidance, in determining what concept the claim is "directed to," we first look to whether the claim recites:

> (1) any judicial exceptions, including "[l]aws of nature, natural phenomena, and abstract ideas," (quoting Alice, 573

[7] *2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50–57 (January 7, 2019).

> U.S. at 216) and/or including certain groupings of abstract ideas (i.e., mathematical concepts, certain methods of organizing human activity such as a fundamental economic practice, or mental processes) (Guidance Step 2A, Prong 1); and
>
> (2) additional elements that integrate the judicial exception into a practical application (*see* MPEP § 2106.05(a)–(c), (e)–(h)) (Guidance Step 2A, Prong 2).

Only if a claim (1) recites a judicial exception and (2) does not integrate that exception into a practical application, do we then look to whether the claim contains an "'inventive concept' sufficient to 'transform'" the claimed judicial exception into a patent-eligible application of the judicial exception. *Alice*, 573 U.S. at 221 (quoting *Mayo*, 566 U.S. at 82). In so doing, we thus consider whether the claim:

> (3) adds a specific limitation beyond the judicial exception that are not "well-understood, routine and conventional in the field" (*see* MPEP § 2106.05(d)); or
>
> (4) simply appends well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception.

(Guidance Step 2B). *See* Guidance, 84 Fed. Reg. at 54–56.

Analysis

Applying the Revised Guidance to the facts on this record, we find that Appellants' claims recite patent-eligible subject matter. Because the same issues are present in each of the claims, we focus our consideration on representative claim 37. The same analysis applied below to claim 37 also applies to the other rejected claims.

I. Guidance Step 2A, Prong 1

The Revised Guidance instructs us first to determine whether any judicial exception to patent eligibility is recited in the claim. The Revised Guidance identifies products of nature as having been identified by the courts as judicial exceptions. 84 Fed. Reg. at 54.

We therefore look to see if the claim recites any judicial exceptions. The Examiner, as already noted, finds that step (c) of the claim that recites aligning and identifying substitutable positions in antibodies, grouping the antibodies, and identifying varying amino acid positions is an abstract idea and a law of nature (Ans. 3–4).

The Specification teaches that "sequences may be aligned by eye, or by employing an alignment program such as one of the CLUSTAL suite of programs" (Spec. 16:23–24). The Specification teaches using the aligned sequences

> to identify a substitutable position of an antibody, the amino acid sequence of that antibody is compared to the sequences of other antibodies belonging to the same group as that antibody. If the identity of that amino acid varies between the different related antibodies of a group at any particular position, that position is a substitutable position of the antibody.

(Spec. 17:19–22). In the context of humanization of antibodies, the Specification teaches that "[b]uilt-in searching engines can be used to search for most similar sequences in terms of amino acid sequence homology" (Spec. 23:6–7).

These computations used to align and group the sequences, along with the use of mathematical operations or mental steps reasonably support the Examiner's finding that the claims recite the judicial exception of a

mathematical concept. *See SAP America, Inc. v. InvestPic, LLC*, 898 F.3d 1161, 1166 (Fed. Cir. 2018) ("The court concluded that the claims . . . are directed to 'performing statistical analysis,' specified using words in the claims and using more technical, mathematical notation in the written description").

Also, we find that claim 37 recites methods and a system for obtaining (step b), aligning (step (c)(i)), grouping (step (c)(ii)), and identifying (step (c)(iii)) biological data associated with antibody sequences. While these methods and system may be performed by a computer (*see* Spec. 16:23–24), they ultimately represent mental processes that a biochemist would undertake to generate a new antibody. As explained by our reviewing court, "analyzing information by steps people go through in their minds, or by mathematical algorithms, without more, [are treated] as essentially mental processes within the abstract-idea category." *Elec. Power Grp., LLC* v. *Alstom S.A.*, 830 F.3d 1350, 1354 (Fed. Cir. 2016). Because claim 37 recites steps involving analyzing information by mathematical algorithms, we find claim 37 recites a mental process in the abstract idea category of judicial exceptions.

II. Guidance Step 2A, Prong 2

A claim that recites a judicial exception requires further analysis to determine if any additional elements integrate the judicial exception into a practical application. *See* 84 Fed. Reg. 54. The 2019 Guidelines explain that additional elements that integrate the judicial exception into a practical application include applying the judicial exception in some meaningful way beyond generally linking the use of the judicial exception to a particular

technological environment. (*See* 84 Fed. Reg. 55, citing *Diamond v. Diehr*, 450 U.S. 175, 184 (1981)).

> As Appellants correctly note
>
> > the end result of the claimed method is not simply an observation or detection of variant antibodies, but instead, the claims recite a number of steps that obtain and identify variant antibodies to achieve a desired outcome (generating a library of antibodies and identifying a novel antibody having a desirable activity).

(App. Br. 10).

That is, the claimed steps of aligning the amino acid sequences, grouping the antibodies based on sequence similarity and identifying varying positions is integrated into a specific method that requires forming a library of variant antibodies that are screened to identify antibodies having desirable activity (*see* Claim 37). We find these final steps analogous to the claims in *Diehr* that recited a method for operating a rubber-molding press including the step of "opening the press automatically when said comparison [of calculated cure time vs. elapsed time] indicates equivalence." *See Diehr*, 450 U.S. at 179 n.5.

We determine that the "making a library" and "screening the variant antibodies" steps represent manufacturing steps that integrate the judicial exceptions into the practical application of obtaining an "antibody having a desirable activity" as required by claim 37. This integration occurs because, as in *Diehr*, the mathematical concepts and abstract ideas recited in claim 37 result in a physical construct, a desirable antibody that has improved properties relative to the starting antibody sequence, such as increased antigen affinity (*see, e.g.*, Claim 49). Specifically, the claimed method is analogous to the *Diehr* step of opening the press because both require a

specific, practical physical act in a particular technological environment that extends the methods beyond mental steps or mathematical analysis. In the instant case, the method does not merely inform the artisan about possible changes in amino acid sequence that might improve the antibody obtained immunization, but actually require the generation of particular improved variant antibodies. Because we conclude that the judicial exceptions recited in claim 37 are integrated into the practical application of methods for creating antibodies with desirable activities, we conclude that claim 37 is directed to patent-eligible subject matter.

We recognize the Examiner's argument that "even the ordered combination of steps in the instant claims does not add significantly more to the exceptions. This is because the steps are well-understood, routine, and conventional" (Ans. 24). However, simply because "a mathematical equation is required to complete the claimed method and system does not doom the claims to abstraction." *Thales Visionix Inc. v. United States*, 850 F.3d 1343, 1349 (Fed. Cir. 2017). The instant claims seek to protect the detailed, and presumably unobvious,[8] method for identifying substitutable positions in antibody, making a library, and screening that library, in order to obtain antibodies having desirable activities.

Therefore, rather than claiming solely an abstract idea or law of nature, claim 37 specifies a particular unobvious approach to such design that results in particular designed and desirable antibodies. *See Thales*, 850 F.3d at 1349 ("The claims specify a particular configuration of inertial sensors and a particular method of using the raw data . . . Far from claiming

[8] We note that the Examiner's obviousness rejection below is reversed.

the equations themselves, the claims seek to protect only the application of physics to the unconventional configuration of sensors as disclosed.")

Alice Step Two

We are persuaded by the Appellants' position that the Examiner does not establish sufficiently that the claims on appeal satisfy *Alice* step one. As such, we need not proceed to *Alice* step two in order to conclude that, on the record before us, it has not been established sufficiently that the claims on appeal fail the *Alice* Test for patent eligibility.

Conclusion of Law

We conclude that claims 37, 39–43, 45–49, and 52 are not directed to patent-ineligible subject matter.

D. 35 U.S.C. § 103(a)[9] over Rader, Watkins, and Wu

The Examiner finds that Rader teaches a process where "Rabbits are immunized with target antigen, antibody genes are isolated, rabbit antibody library is constructed, selection for binding to antigen occurs, humanization via CDR grafting is performed, and finally humanized antibodies are selected for target antigen binding" (Ans. 4–5). The Examiner finds Rader teaches alignment and comparison of "3 rabbit antibody clone sequences" as well as issues about anti-idiotypic response (Ans. 5).

The Examiner acknowledges that Rader "does not teach use of the noted CDR variations to identify substitutable positions and use the amino

[9] The Examiner acknowledges that the Moe patent does "not receive the priority date of 06/23/2004 with respect to the taught sections, and, in view of Applicant's arguments above over their own priority, should be removed as prior art" (Ans. 26).

acids represented to construct an antibody library for screening for any purpose" (Ans. 5).

The Examiner finds Watkins teaches the ordinary artisan "routinely made and used libraries of antibody CDR variants and screened them to optimize activity" (Ans. 6). The Examiner finds Wu teaches the "use of CDR variant combinatorial antibody libraries to optimize antibody function" (Ans. 7). The Examiner finds Wu "aligned and assessed differences between related antibody CDRs" (Ans. 7). The Examiner acknowledged that Wu "uses a less sequence-guided approach in their screening process than the method of instant claims" but finds "smaller library size allowed for easier screening and so contribution of all six CDRs could be assessed and beneficial mutations were found in all six CDRs" (Ans. 7).

The Examiner finds the combination obvious because the artisan would have been "motivated to apply the sequence comparison and library screening techniques in the prior art above in order to find improved therapeutic humanized antibodies" (Ans. 8).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that Rader, Watkins, and Wu render claim 37 obvious?

Findings of Fact

1. Rader teaches the use of "phage display technology to select and humanize antibodies from rabbits that were immunized with human A33 antigen which is a target antigen for the immunotherapy of colon cancer" (Rader 13668, abstract).

2. Figure 1 of Rader is reproduced below:

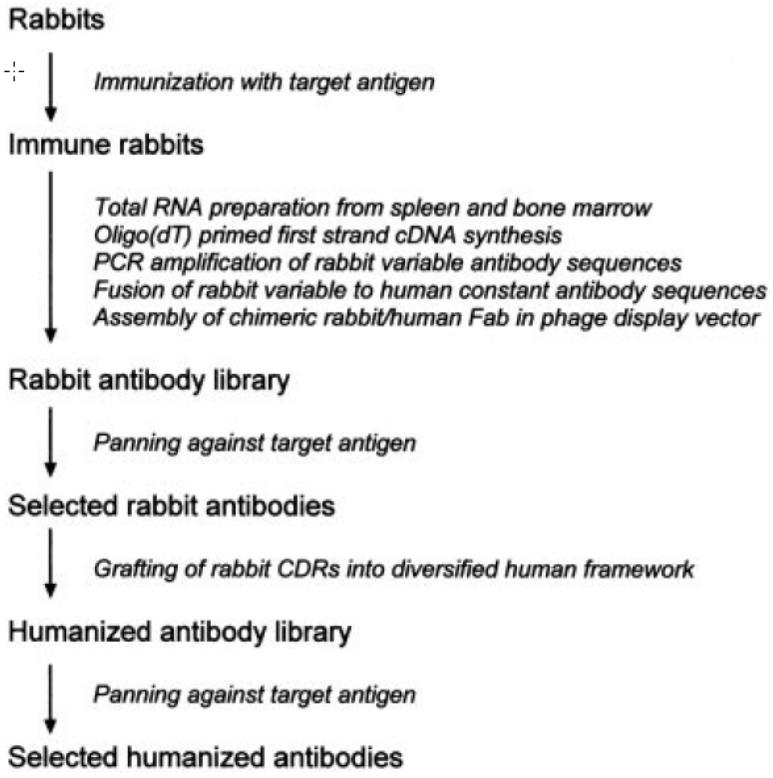

Figure 1 is a "[f]low chart outlining the process of generating and humanizing rabbit antibodies directed to a target antigen" (Rader 13670, col. 2).

3. Figure 2 of Rader is reproduced, in part, below:

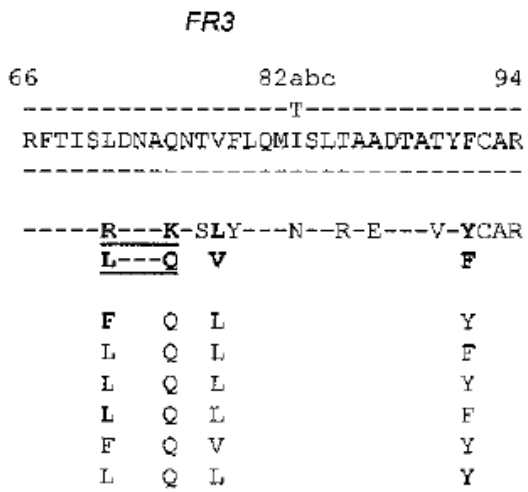

Figure 2 depicts "frameworks (FRs) . . . [of] VH sequences. Dashes indicate identical amino acids. The humanized library with diversified human FRs . . . is shown in the center. Diversified positions are shown in bold type. Underlined positions indicate a coupled diversification that limits the selection to either all human or all rabbit sequence" (Rader 13671).

4. Rader teaches:

> Analysis of sera from the patients revealed evidence for an anti-idiotypic immune response, *i.e.* the sera contained antibodies that recognized the antigenbinding site of humanized antibody A33. Administration of an equally potent humanized antibody that is unreactive to the anti-idiotypic immune response generated by humanized antibody A33 would allow therapy to continue.

(Rader 13675, col. 1).

5. Rader teaches "our humanized antibodies derived from the rabbit antibody repertoire complement humanized antibody A33 derived from the mouse antibody repertoire" (Rader 13675, col. 2).

6. Watkins teaches:

> Libraries of CDR variants containing single amino acid substitutions were generated (Example II). The libraries were screened for binding to a cryptic collagen site, and single amino acid mutations having beneficial activity were identified. Combinatorial mutants, in which two or more variant CD Rs containing at ieast one amino acid substitution relative to parental HUIV26 or HUI77 CDRs were combined and screened for activity (Example III). A number of combinatorial mutants having optimized activity for binding to a cryptic collagen site were identified.

(Watkins ¶ 44).

7. Wu teaches a "protein engineering strategy based on efficient and focused mutagenesis implemented by codon-based mutagenesis was

developed" (Wu 6037, abstract).

8. Wu teaches "phage-expressed antibody libraries for all six lg heavy and light chain complementarity-determining regions were expressed and screened . . . variants in these libraries each contained a single mutation, and all 20 amino acids were introduced at each complementarity-determining region residue, resulting in the expression of 2,336 unique clones" (Wu 6037, abstract).

9. Wu teaches "variants with enhanced affinity were identified rapidly and required the synthesis of only 2,592 unique variants" (Wu 6037, abstract).

10. Wu teaches:

> **Construction of CDR Libraries**. Using the numbering system of Kabat et al. . . . the residues chosen for mutagenesis of the CDRs (see Table 2) were: Gln^{24}-Tyr^{36} in light chain CDRl (L1); Leu^{46}-Ser^{56} in light chain CDR2 (L2); Gln^{89}-Thr^{97} in light chain CDR3 (L3); Gly^{26}-Ser^{35} in heavy chain CDR1 (H1); Trp^{47}-Gly^{65} in heavy chain CDR2 (H2); and Ala^{93}-Tyr^{102} in heavy chain CDR3 (H3). Libraries were created for each CDR, with the oligonucleotides designed to mutate a single CDR residue in each clone.

(Wu 6038, col. 1).

11. Table 2 of Wu is reproduced below:

Table 2. Identification of beneficial mutations from Vitaxin primary libraries

Chain	Library	Sequence	k_{on} ($\times 10^4$), $M^{-1}\,s^{-1}$	k_{off} ($\times 10^{-3}$), s^{-1}	K_d, nM
	Vitaxin		18.0	4.97	27.6
H	CDR1	G F T F S S Y D M S			
	T27	**T**	n.d.	n.d.	n.d.
	W29	**W**	n.d.	n.d.	n.d.
	L30	**L**	n.d.	n.d.	n.d.
H	CDR2a	W V A K V S S G G G			
	K52	**K**	17.8	2.18	12.2
H	CDR2b	S T Y Y L D T V Q G			
	P60	**P**	31.8	1.85	5.8
	E64	**E**	n.d.	n.d.	n.d.
H	CDR3	A R H N Y G S F A Y			
	H97	**H**	22.0	3.03	13.8
	Y100	**Y**	17.5	2.51	14.3
	D101	**D**	n.d.	n.d.	n.d.
	Y101	**Y**	21.8	0.48	2.2
	S102	**S**	24.2	1.44	6.0
	T102	**T**	24.6	1.43	5.8
	D102	**D**	27.6	0.97	3.5
	E102	**E**	n.d.	n.d.	n.d.
	M102	**M**	n.d.	n.d.	n.d.
	G102	**G**	16.1	2.01	12.5
	A102	**A**	27.5	2.27	8.3
L	CDR1	Q A S Q S I S N H L H W Y			
	F32	**F**	16.7	0.42	2.5
L	CDR2	L L I R Y R S Q S I S			
	S51	**S**	n.d.	n.d.	n.d.
L	CDR3	Q Q S G S W P H T			
	N92	**N**	23.6	1.35	5.7
	T92	**T**	n.d.	n.d.	n.d.
	L96	**L**	24.3	2.23	9.2
	Q96	**Q**	n.d.	n.d.	n.d.

n.d., not determined.

Table 2 shows the antibody "variants all displayed a lower Ka than the Vitaxin parent molecule" (Wu 6039–40).

Principles of Law

A prima facie case for obviousness "requires a suggestion of all limitations in a claim," *CFMT, Inc. v. Yieldup Int'l Corp*., 349 F.3d 1333, 1342 (Fed. Cir. 2003) and "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex In*c., 550 U.S. 398, 418 (2007).

Analysis

Appellants contend that the Examiner acknowledges Rader doesn't teach "(a) identifying substitutable positions and (b) substituting those positions to produce a library" (App. Br. 12; *cf.* Ans. 5). Appellants contend

> Watkins and Wu fail to provide what Rader lacks. Specifically, Watkins and Wu do not actually teach identifying substitutable positions and substituting those positions to produce a library. Rather, those publications simply show that one of ordinary skill in the art can make a library of variants by random methods and then screen the library. Steps (c) and (d) of claim 37, i.e., identifying substitutable positions using sequence alignments and making a library of candidate antibodies that comprise substitutions at the substitutable positions are not taught or suggested by either of the publications.

(App. Br. 12–13).

The Examiner responds that "Wu clearly shows beneficial mutations identified via screening in all three light chain CDRs, again, totaling to more than five potential substitutions" (Ans. 26). The Examiner finds the resulting

> antibodies discussed in Table 3 of Wu were not made by random mutagenesis. This is clear just from the table's title identification of optimal combinatorial mutations. In a

> combinatorial approach, the changes are previously known. Therefore, the mutants of Table 3 of Wu do not carry random mutations but the beneficial mutations identified in the first screen of Wu (Table 2). Said another way, Applicant must consider that Wu teaches both a primary screen and a secondary screen after recombining beneficial mutation identified in the primary screen.

(Ans. 27).

We agree with Appellants. Claim 37, step (c) requires a step of grouping aligned antibodies and "identifying positions at which the amino acid varies" followed by step (d) of making substitutions at those variant positions in a library of candidate antibodies. While Rader and Wu both show alignments of antibodies, and these alignments have positions that vary (FF 3, 11), neither Rader nor Wu teaches varying the positions based on variant positions in the disclosed alignment as recited in step (c) of the claim. Rader clearly simply performs an alignment, but does not teach the step of "grouping the antibodies according to their sequence similarity to produce groups of related antibodies" (FF 3). Wu teaches generating a candidate antibody library, but generates this library by introducing mutations at every position in the CDR, rather than restricting the introduced mutations to variant positions as required by claim 37 (FF 10).

Table 2 of Wu shows the results of the random screening of every position in the CDR (FF 11). The Examiner provides no persuasive reason why the ordinary artisan would use Wu's alignment of the experimental results to perform a further mutation process at the specific positions identified. That is, Table 2 of Wu is the end of the process, not an intermediate step as in claim 37. We therefore agree with Appellants that "there is no clear path from those references to toward the claimed method"

(Reply Br. 4).

Conclusion of Law

A preponderance of the evidence of record does not support the Examiner's conclusion that Rader, Watkins, and Wu render claim 37 obvious. The Examiner's obviousness rejection with respect to claims 39–43, 45–49, and 52, which depend from claim 37, is reversed for the same reasons. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.").

CONCLUSION

In summary:

Claim(s) Rejected	Basis	Affirmed	Reversed
45, 49	§ 112(b)		45, 49
45	§ 112 (d)		45
37, 39–43, 45–49, and 52	§ 101		37, 39–43, 45–49, and 52
37, 39–43, 45–49, and 52	§ 103(a)		37, 39–43, 45–49, and 52
Overall Outcome			37, 39–43, 45–49, and 52

REVERSED