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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/433,069	05/12/2006	Thomas Kodadek	UTSD:1578US	9065

108197 7590 10/28/2016
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ART UNIT	PAPER NUMBER
1678	

NOTIFICATION DATE	DELIVERY MODE
10/28/2016	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte THOMAS KODADEK[1]

Appeal 2015-005364
Application 11,433,069
Technology Center 1600

Before MELANIE L. McCOLLUM, ULRIKE W. JENKS, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a method of screening an antibody population from an individual suspected of or having a disease. The Examiner entered final rejections for obviousness, indefiniteness, lacking sufficient written descriptive support, and as containing nonstatutory subject matter.[2] We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the Real Party in Interest as the Board of Regents, University of Texas System, Austin, TX. App. Br. 3.
[2] The rejection under 35 U.S.C. § 112, second paragraph, was withdrawn (*see* Advisory Action, mailed May 14, 2014).

STATEMENT OF THE CASE

The Specification discloses:

> The present invention provides methods of using synthetic molecules, *i.e.,* ligands, that bind ligand binding moieties, such as proteins, nucleic acids, carbohydrates, or non-adherent cells present in complex biological mixtures, as biomarkers for a particular physiological state(s). The synthetic molecules may have not been previously selected to bind ligand binding moieties, which includes biomarkers present in a sample. In some cases the identities of ligand binding moieties known prior to the process. The invention includes methods comprising: (a) constructing an array of synthetic molecules having a plurality of structures; (b) contacting said array with a complex biological mixture obtained from animals or cells that exhibit a physiological state of interest, resulting in the capture of certain biological molecules or cells by certain molecules immobilized on the array; (c) assessing binding of certain captured molecules or cells to this array through the use of a labeled reagent that binds specifically to a given class of captured molecules or proteins; and (d) comparison of this binding pattern with the binding pattern of an appropriate control sample that does not represent the physiological state of interest. Aspects of the invention include constructing the array from synthetic molecules not previously selected to bind any particular molecule or cell in the sample of interest. In certain embodiments, the array of synthetic molecules is an array of peptoids (peptoid-like oligomers) derived from a combinatorial library. The complex biological mixture can be a serum sample obtained from an animal or patient with or suspected of having a disease. Binding of serum antibodies to the array is typically quantified by subsequent incubation with a fluorescently labeled secondary antibody. Peptoids that capture antibodies

> enriched in the diseased state are identified by comparison of the pattern of antibody binding of the two samples to the arrays.

(Spec. ¶ 9).

The Issues

The following rejections are before us to review:

Claims 1, 2, 6, 14, 22, 24–34, and 66–68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Francoeur,[3] Thompson,[4] Charych,[5] and Granoff[6] (Ans. 13).

Claims 1, 2, 6, 14, 22, 24–34, and 66–68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Robinson,[7] Heine,[8] Barry,[9] and Charych (Ans. 16).

Claim 68 is rejected under 35 U.S.C. § 112, first paragraph as lacking written descriptive support for the claimed subject matter (Ans. 4).

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[3] Ann-Michele Francoeur, U.S. Pat. No. 4,880,750, issued Nov. 14, 1989 ("Francoeur").
[4] Vicki S. Thompson et al., U.S. Pat. No. 6,989,276 B2, issued Jan. 24, 2006 ("Thompson").
[5] Deborah Charych et al., US 2002/0055125, published May 9, 2002 ("Charych").
[6] Dan M. Granoff and Gregory R. Moe, U.S. Pat. No. 6,030,619, issued Feb. 29, 2000 ("Granoff").
[7] William H. Robinson et al., US 2003/0003516 A1, published Jan. 2, 2003 ("Robinson").
[8] Niklas Heine et al., *Synthesis and screening of peptoid arrays on cellulose membranes*, 59 Tetrahedron 9919–9930 (2003) ("Heine").
[9] Richard Barry et al., US 2002/0055186 A1, published May 9, 2002 ("Barry").

Claims 1, 2, 6, 14, 22, 24–34, and 68 are rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter (Ans. 2).

Claims 1 and 68 illustrate the appealed subject matter and reads as follows:

> 1. A method of screening an antibody population in a complex biological sample from a subject suspected of or having a disease comprising:
>
> (a) providing an array of peptoid ligands having a plurality of random-structures, wherein said peptoid ligands are not preselected based on known reactivity to said antibody population;
>
> (b) contacting said array with the complex biological sample from the subject comprising an antibody population;
>
> (c) assessing binding of said antibody population to said array;
>
> (d) comparing the binding in step (c) with the binding of a control antibody population to an identical control array, said control antibody population representing a healthy or diseased sample, wherein comparing identifies antibodies in the antibody population in said complex biological sample that are associated with the disease.
>
> 68. The method of claim 1, further comprising
>
> (a) providing a supplementary array comprising at least one peptoid ligand identified as binding to an antibody in the complex biological sample, but not binding to an antibody in the control antibody population;
>
> (b) exposing the supplementary array to a patient sample potentially containing disease associated antibodies;
>
> (c) detecting any disease associated antibodies bound to the at least one peptoid ligand on the supplemental array; and

> (d) comparing the binding in step (c) with the binding of a second control antibody population to said array, said second control antibody population representing a healthy or diseased sample, wherein said comparing step screens the antibody population in the complex biological sample for the presence or absence of disease associated antibodies.

App. Br. Claims App'x. 22.

Obviousness over Francoeur, Thompson, Charych, and Granoff

The issue is: Does the preponderance of evidence of record support the Examiner's finding that the teachings of the cited references suggest the method of claim 1?

Findings of Fact

FF 1. Francoeur teaches

> The instant invention, termed antibody fingerprinting, presents a general identification method whereby animate and inanimate objects can be identified. It is premised on the hithertofore unrealized discovery that humans, as well as animals generally have present in their body, a heretofore unknown set of individual specific, or IS antibodies [(individual-specific antibodies)]. When an individual's body fluid (or solids) containing IS antibodies, is screened against a panel (an n-dimensional array where n is typically 1 or 2), of multiple antigens (typically greater than 10,000 different antigens), distinct antigen-antibody complexes are formed. The antigen-antibody complexes are detected using an appropriate antibody-binding detector molecule, typically radioactive or enzymes that give a colored product on reaction with substrate. The antigen-antibody reactivity profile, or antibody fingerprint, can be used to identify individual humans or animals.

Francoeur 3:56–4:5.

FF 2. Francoeur teaches that a "basic immunological method, as applied to the identification of individuals" includes:

> (a) Obtaining an effective concentration of IS antibodies, preferably, in solution, from an individual's body fluid, such as urine, plasma, serum, saliva, perspiration, semen, or lung washings, or from an individual's body solids such as tissue or feces. . . . .
>
> (b) Reacting the antibody solution obtained in (a) with an effective panel of antigens where panel refers to an n-dimensional array of antigens, where n is typically one or two, to form antigen-antibody complexes. . . .
>
> (c) detecting the antigen-antibody complexes with an effective amount of an appropriate detector molecule.
>
> The identity of an individual is established by comparing the resulting antigen-antibody reactivity profile, or antibody fingerprint, with that of an earlier obtained profile known to be characteristic of the individual. Similarly, individuals or inanimate objects, such as blood transfusions or tissues obtained after an air crash, may be distinguished by comparing antibody fingerprints obtained from each.

Id. at 7:3–50.

FF 3. Francoeur teaches that in using the antibody fingerprinting method in humans, the inventors observed

> It is apparent that the fingerprints are virtually identical at early and late times, and are constant over a multiyear period. The individual whose fingerprints are shown . . . became gravely ill (vasculitis), and his fingerprint is obtained during this condition . . . . It is apparent that during the illness, the amount of antibody-antigen complexes was increased and thus the intensity of the fingerprint was stronger than when he was well. Minor changes in the fingerprint were detected.

Id. at 12:49–56.

FF 4. Thompson teaches

> An illustrative embodiment of the invention comprises a method for analyzing biological material including individual-specific antibodies, comprising: forming an array of multiple antigens by attaching the multiple antigens to the surface of a solid support in a preselected pattern such that the locations of the multiple antigens are known; obtaining a sample of the biological material and contacting the array with the sample such that a portion of the individual-specific antibodies contained in the sample reacts with and binds to antigens in the array, thereby forming immune complexes; washing the solid support containing the immune complexes such that antibodies in the sample that do not react with and bind to the antigens in the array are removed; and detecting the immune complexes and determining the locations thereof such that an antibody profile is obtained.

Thompson 3:37–51.

FF 5. Thompson discloses "[f]ew studies have been conducted on individuals with long-term diseases. Preliminary results, however, indicate that, although a few extra bands may appear, the overall pattern remains intact." *Id.* at 2:40–43.

FF 6. Charych teaches

> [T]he present invention provides peptidomimetic protein-binding arrays, their manufacture, use, and application. The protein-binding array elements of the invention include a peptidomimetic segment, an anchor segment and a linker segment connecting the peptidomimetic and anchor segment. The invention contemplates peptidomimetic array element library synthesis, distribution, and spotting of array elements onto solid planar substrates, labeling of complex protein mixtures, and the analysis of differential protein binding to the array.

Charych ¶ 8.

FF 7. Charych teaches

> A further aspect of the present invention pertains to a method of performing a differential binding assay. The method involves labeling proteins in a protein-containing biological sample solution, contacting an aliquot of the labeled protein-containing biological sample solution with an array as described herein, and analyzing the array to determine differential binding of proteins in the sample to protein-binding agents of the array.

Id. ¶ 12.

Principle of Law

An invention is not patentable under 35 U.S.C. § 103 if it is obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). Under § 103: the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). A central question in analyzing obviousness is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417.

> Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention. A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination.

Syntex (U.S.A.) LLC v. Apotex, Inc., 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citations omitted).

Analysis

The Examiner provides sound fact-based reasoning for combining Francoeur, Thompson, Charych, and Granoff. We adopt and incorporate by reference the Examiner's findings and conclusions as presented in the Final Action mailed June 6, 2013 and Answer. We address the arguments raised by Appellant on appeal below.

Appellant argues that Francoeur's "fingerprint assay is about identifying antigens, not antibodies" and that the reference does not teach profiling disease because it teaches antibodies could only be useful in diagnostics "'on purification.'" App. Br. 13. Appellant further argues that Francoeur does not disclose profiling of disease because Francoeur does not teach that "the [antigen] ***pattern*** changed," rather Francoeur observed only an increase in the immune complexes as the disease progressed. *Id.* at 13–14.

Appellant argues that Charych likewise does not teach using antibodies to profile disease, but rather teaches use of "other types of molecules, *e.g.*, cancer or infectious disease proteins." For support regarding what Charych teaches, Appellant relies on the background section of Thompson for its disclosures regarding the teachings of Francoeur. *Id.* at 15. Specifically, Appellant points to Thompson's disclosures, *inter alia*, "[***a***]***n individual's*** [***antibody***] ***profile is apparently stable for life and is not affected by short-term illnesses***'" as a teaching away and the further

statement "***[f]ew studies have been conducted on individuals with long-term diseases. Preliminary results, however, indicate that, although a few extra bands may appear, the overall pattern remains intact***" as evidence that "Francoeur disclosed that antibodies could not be useful as a 'fingerprint' for a disease state," that Thompson "adopted th[is] same view" by citing Francoeur and Charych "provides no evidence to the contrary." *Id.* at 15–16.

Finally, Appellant argues that "making changes to the cited art in order to arrive at the present invention would run directly contrary to the clear teachings therein." *Id.* at 17–18.

We are not persuaded that the Examiner erred in rejecting claim 1 over Francoeur, Thompson, Charych, and Granoff. Francoeur teaches a blocked fingerprint assay with a "basic immunological method" similar to that of claim 1. FF 1–2. Appellant's argument that Francoeur teaches "antigens, not antibodies" is misguided as the antigens taught in Francoeur's method serve the exact same purpose as the peptoid ligands of the instant invention: the Francoeur antigens are exposed to and bind to antibodies in the biological sample to create a profile of the antibodies present in the tested individual. *Id.*; Spec. ¶ 3: "In particular, the invention relates to compositions and methods for profiling or fingerprinting proteins in a target sample, such as antibodies." Charych teaches use of peptoid ligands to assay antibodies (FF 6–7); without any evidence to the contrary, we agree with the Examiner that substitution of peptoid ligands for the antigens of Francoeur is a straightforward process within the ability of one of ordinary skill in the art, as is antibody purification for diagnostic use. *See In re Fout*,

675 F.2d 297, 301 (CCPA 1982) ("Because both [references] teach a method for separating caffeine from oil, it would have been prima facie obvious to substitute one method for the other. Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious.").

Appellant's argument that Francoeur and Thompson fail to teach disease profiling because they do not disclose differences in the "pattern" of the antibody profile is not persuasive because claim 1 does not recite detecting an antibody expression "pattern," but rather recites "identif[ication of] antibodies in the antibody population in said complex biological sample that are associated with the disease." Thus, the scope of claim 1 is directed at what Francoeur and Thompson teach: use of arrays to determine the presence of antibodies. FF 1–4.

Regarding the teaching of disease profiling, Francoeur and Thompson both disclose that "extra bands" appear in the antibody profiles of samples taken from individuals with a long-term disease. FF 5. Moreover Francoeur teaches "the amount of antibody-antigen complexes was increased and thus the intensity of the fingerprint was stronger" in a patient with vasculitis (FF 3). We are not persuaded that the cited references teach away from "applying a[] peptoid-antibody profile for the purpose of distinguishing disease[] from healthy states" (App. Br. 16) because they do not "suggest[] that the developments flowing from [their] disclosures are unlikely to produce the objective of the applicant's invention. *Syntex*, 407 F.3d at 1380. Accordingly, we affirm the rejection of claim 1 over Francoeur, Thompson, Charych, and Granoff. Claims 2, 6, 14, 22, 24–34, and 66–68 have not been

argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

Obviousness over Robinson, Heine, Barry, and Charych.

The issue is: Does the preponderance of evidence of record support the Examiner's finding that the teachings of the cited references suggest the method of claim 1?

Findings of Fact

FF 8. Robinson discloses

> For the purposes of the invention, arrays of autoantigens and autoantigen-derived epitopes can be used to determine a patient's antibody specificity profile for the identification or determination of: 1. patients likely to develop disease; 2. patients likely to develop more or less severe disease; 3. patients likely to respond to a particular therapy, or to have an adverse event related to a particular therapy; 4. patient-specific therapy; and, 5. whether a particular therapeutic intervention has been successful, unsuccessful, or detrimental. An autoantigen array comprises the various autoantigens either known to be associated with disease, suspected to be associated with a particular disease, or a library of potential autoantigens. An autoantigen array, in one instance may include autoantigens optimized for a particular disease, while in another instance may include a library of unknown antigens to identify targets of the antibody response in patients with a disease.

Robinson ¶ 47.

FF 9. Robinson recites in Claim 30:

> 30. A method for treating autoimmune disease comprising
> (a) determining the epitope specificity profile of a patient comprising the steps of:
> (1) preparing an epitope array;

> (2) physically contacting the epitope array from step (1) with a patient sample comprising antibodies;
> (3) identifying the disease associated epitopes within the array that bind to antibodies within the patient sample from step (2);
> (4) comparing the antibodies bound to the disease associated epitopes in step (3) with (i) antibodies binding to the disease associated epitopes within the array of step (1) wherein the antibodies are known to be associated with the disease; and, (ii) antibodies binding to the disease associated epitopes within the array of step (1) wherein the antibodies are not associated with the disease;;(b) designing a patient specific treatment regimen based upon the epitope specificity profile of step (a) comprising the steps of: (1) determining the epitopes bound by the antibodies in the patient sample; and, (2) administering one or more epitopes to the patient.

Analysis

The Examiner provides sound fact-based reasoning for combining Robinson, Heine, Barry, and Charych. We address the arguments raised by Appellant on appeal below.

Appellant argues that the cited references fail to teach the claimed invention. Appellant argues:

> Robinson *et al.* does not use a random library, but rather, an array with known immunogenic components having a high affinity for specific antibodies already associated with a particular disease. These antigens were selected for their biological properties and thus are not "random" arrays. In contrast, the claimed invention uses peptoids with random

> structures that are not known as "antigens" and are not biased to a particular antibody or a particular disease state.

App. Br. 18–19.

Appellant argues that Robinson's teaching that "[***a***]***n autoantigen array***, in one instance may include autoantigens optimized for a particular disease, ***while in another instance may include a library of unknown antigens to identify targets of the antibody response in patients with a disease***" is a "single passing comment" and because "every single example offered by this reference deals with the use[] of preselected or biased libraries – not random libraries . . . this document would do nothing to convince the skilled artisan that random peptoid arrays could or should be used to distinguish diseased from healthy subjects." *Id.* at 19–20.

Appellant further argues none of Heine, Barry or Charych supply teaching on use of a "'random' library" because Heine "uses an isolated and purified monoclonal antibody," Barry "requires the array to comprise capture agents (preferably antibodies) that are specific for a target peptide fragment in a sample," and Charych "shows binding to a known, selected antibody" *Id.* at 19–21. Finally, Appellant argues Charych "does not provide any teaching of screens for unknown antibodies associated with a disease, and certainly no comparison of healthy and diseased samples except in the case of labeled (and known) proteins which are screened against the library." *Id.* at 20.

We are not persuaded that the Examiner erred in rejecting claim 1 over Robinson, Heine, Barry, and Charych. Robinson teaches that arrays of autoantigens and autoantigen-derived epitopes can be used to determine a

patient's antibody specificity profile for the purpose of disease diagnosis and therapy. FF 8. Robinson discloses that the array may be prepared from autoantigens that are "known to be associated with disease," "suspected to be associated with a particular disease" or a "library of potential autoantigens" (e.g., proteins of yet undetermined reactivity). *Id.* Robinson further discloses that the library may include "unknown antigens to identify targets of the antibody response in patients with a disease." *Id.* Robinson claims a method of treating autoimmune disease "wherein the antibodies are not associated with the disease." FF 9. In light of these specific disclosures, and without evidence to the contrary, we find Appellant's attorney argument alone insufficient to overcome the Examiner's strong prima facie case of obviousness. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("[A]ttorney argument [is] not the kind of factual evidence that is required to rebut a prima facie case of obviousness"). Accordingly, we affirm the rejection of claim 1 over Robinson, Heine, Barry, and Charych. Claims 2, 6, 14, 22, 24–34, and 66–68 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

Written Description

The Examiner finds that with respect to claim 68:

> The claim is drawn to a method of screening for antibodies associated with disease that bind to an entirely undefined identified subpopulation of an entirely undefined random population of peptoid ligands that do not bind control antibodies. The invention as claimed encompasses all known or potential diseases or broad categories of diseases, any antibody populations, and any genus of peptoid ligands of any

> structure since virtually any antibody or peptoid can be screened from any patient sample. The specification does not teach how any particular peptoid ligand structure or antibody binding thereto is definitively or even predictably associated with any particular disease. Thus, absent further written description and guidance from appellant, one would not know or be able to predict what peptoid ligands specifically bind to the relevant antibodies, do not bind to control antibodies, and predictably function as associated in the assay with any particular disease . . . Furthermore, the specification does not teach how to associate a particular disease with any particular "fingerprint" of antibody profile because no structure, genus, or species of peptoid(s) performing the function of binding relevant antibodies for any particular disease and not binding control antibodies is disclosed, only numbers of undefined random peptoids which differ in signal intensity among individuals or a limited number of individuals are disclosed.

Ans. 4–6.

> Appellant responds:
>
> The subject matter here lies in the use of a peptoid array of sufficient complexity – any peptoid array – to distinguish diseased from healthy patients. Clearly, appellant has not done this with specific patterns of specific peptoids and correlated them with specific disease states. However, the ability of peptoid arrays to provide this level of discrimination in general is the subject matter of the invention, and not some ***particular*** set of peptoids for use in diagnosing a ***particular*** disease.

App. Br. 8.

Appellant further argues that the differences between claim 68 and claim 1, which is not rejected, are "inconsequential" because it "merely extends from step (d) of claim 1, and puts into play the relevant peptoid(s) bound[] to

disease-specific antibodies from claim 1 in a second detection. Reply Br. 4–5. According to Appellant, [n]o particular disease state or peptoid needs to be identified because the claim is *generic* to the endeavor of correlating antibodies and peptoids with diseases." *Id.* at 5.

We find that the Examiner has the better position. We agree with Appellant that claim 68 extends from the final step of claim 1, and explains what next steps could be taken with peptoids that are identified as associated with disease using the method of claim 1. However, Appellant has not disclosed any such peptide as required to enable one of skill in the art to practice the claimed invention in compliance with § 112. *See University of Rochester v. G.D. Searle & Co.,* 358 F.3d 916, 926, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004) ([I]t is undisputed that the . . . patent does not disclose any compounds that can be used in its claimed methods. The claimed methods thus cannot be practiced based on the patent's specification, even considering the knowledge of one skilled in the art. No compounds that will perform the claimed method are disclosed, nor has any evidence been shown that such a compound was known.") Appellant acknowledges that he has not performed the claimed method "with specific patterns of specific peptoids and correlated them with specific disease states." App. Br. 8. Such effort would be necessary in order to claim use of that antibody in the claimed method. *See Noelle v. Lederman*, 355 F.3d 1343, 1349 (2004), in which the Federal Circuit found that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that

described antigen." Given that Appellant has not undertaken this work, but the scope of claim 68 includes the fruits of such labor, we affirm the written description rejection of claim 68.

Nonstatutory Subject Matter

The Examiner finds that

> [T]he claimed invention is directed to a non-statutory subject matter because it is not a patent-eligible practical application of a law of nature or of a naturally occurring correlation, i.e.[,] of a natural principle. The claims are directed to a naturally occurring correlation between a disease and associated levels or presence of an antibody biomarker profile . . . [w]hen the claims are considered as a whole, the steps taken together amount to no more than recognizing the natural principle itself.

Final Act. 4–5; *see* Ans. 3–4. The Examiner reached this conclusion by applying the test set out in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012).

Appellant argues the claims "provide a particular transformation – they require use of an array to interrogate a biological sample, during which both the sample and the array are transformed." App. Br. 5. Appellant argues the law of nature at issue, "whether a patient has [] antibodies reflective of a disease state – is quite practically applied in [] step (d) [of the method]" and that the claim "provides more than a mere 'concept' as it solves the problem of diagnosis in a tangible way – antibodies bound to an array." *Id.* Appellant further argues the claimed "methods rely on novel, man-made antigen surrogates (e.g., synthetic ligands/peptoids) that are being recognized by immune reactivities, *i.e.*, antibodies," and that step (a) "is 'loaded' with man-made features that clearly go beyond any 'law of nature'"

because the claim requires "a plurality of random structures that ***are not preselected*** based upon a known reactivity to an antibody population." *Id.* at 5–7. According to Appellant, "[t]he only 'law of nature' present under the current facts relates to patients that have or do not have a particular disease that produces potentially detectable antibodies" but the "'end product' of the claim - a comparison that leads to identification of antibodies f[or]m a diseased sample that bind to man-made ligands on an array versus a control sample [-] does ***not*** create a monopoly on a law of nature." *Id.* at 6–7.

We agree with the Examiner that, under the two-step test of *Mayo*, the claims are not directed to patent-eligible subject matter. The *Mayo* court applied its test to claims that are similar to those of the instant application. In *Mayo*, the claimed invention was a "method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder" comprising administering a certain class of drug and then determining the level of 6-thioguanine (6-TG) in a patient, where a level of 6-TG below or above certain amounts indicated a need to increase or decrease, respectively, the drug dosage. *Mayo*, 122 S. Ct. at 1295.

Claim 1 of the instant application is similar, in that it is directed to a method of screening an antibody population in a biological sample and comparing the results to those of a control antibody population to assess whether antibodies associated with disease are present.

The *Mayo* Court concluded that the claims at issue in that case "set forth laws of nature--namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 1296.

Similarly here, as acknowledged by Appellant, claim 1 on appeal sets forth a law of nature--namely, the relationship between the level of expression of detectable antibodies that is made by a test subject and whether that subject has or does not have a disease. App. Br. 6. Under the first step of the *Mayo* test, claim 1 on appeal is directed to a law of nature or natural phenomenon.

The *Mayo* Court next turned to the question "[w]hat else is there in the claims before us?" *Id.* at 1297. The claims in *Mayo* included an "'administering'" step, a "'determining'" step, and a "'wherein'" clause. *Id.* The Court concluded that "[t]he upshot is that the three steps simply tell doctors to gather data from which they may draw an inference in light of the correlations." *Id.* at 1298. In other words, the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. *Id.* The Court concluded that "the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." *Id.*

Like the steps of the claims *in Mayo,* the manipulative steps of claim 1 on appeal also "consist of well-understood, routine, conventional activity already engaged in by the scientific community." *Id.*

Providing an array of peptoid ligands is known in the art as shown by Charych in ¶¶ 33–69, which summarizes methods for making "Protein-Binding Agent Arrays."

Using arrays with a plurality of random ligands that are not preselected based on known reactivity to antibody populations is also routine, as shown by Thompson in 5:63–9:24, teaching methods for constructing arrays (e.g., 7:36–38 "[t]he antigens, whether selected randomly or nonrandomly, are disposed on the solid support to result in the array") as well as methods of assaying the binding of antibodies by contacting the array with a sample, followed by assessing the binding and comparing the binding to a control population.

The final step of identifying the screened antigens to identify antibodies in a biological sample that are associated with a disease is also routine, as shown by Robinson ¶ 71:

> The means for identifying the disease-associated antigens within the array that bind to the antibodies within the patient sample utilize methods for detection that are known in the art. Those methods of identification may include pre-labeling the sample directly or indirectly; adding a second stage antibody that binds to the antibodies or to an indirect label, e.g. labeled goat anti-human serum, rat antimouse, and the like. Other methods of identification include analysis of addressable elements such as beads, nanoparticles, tags, cleavable tags and other physical properties of or conferred upon the elements within the array. Varying concentrations of a single epitope may be present in order to facilitate quantitation of the bound antibody.

Robinson ¶ 71.

Thus, when claim 1 is considered as an ordered combination, it informs a relevant audience of certain laws of nature: specifically, that the production of antibodies by persons having a disease can be used to identify those persons as having the disease. Any additional

steps of claim 1 consist of well-understood, routine, conventional activity already engaged in by the scientific community as shown in Charych, Thompson, and Robinson.

We conclude that, under the *Mayo* test, claim 1 is directed to patent ineligible subject matter. The rejection of claim 1 under 35 U.S.C. § 101 is affirmed. Claims 2, 6, 14, 22, 14–34, and 68 were not argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejection of claims 1, 2, 6, 14, 22, 24–34, and 66–68 under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Francoeur, Thompson, Charych, and Granoff.

We affirm the rejection of claims 1, 2, 6, 14, 22, 24–34, and 66–68 under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Robinson, Heine, Barry, and Charych.

We affirm the rejection of claim 68 under 35 U.S.C. § 112, first paragraph, as lacking written descriptive support for the claimed subject matter.

Claims 1, 2, 6, 14, 22, 24–34, and 68 are rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter.

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).

AFFIRMED