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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STEPHEN ALBERT JOHNSTON,
PHILLIP STAFFORD, and NEAL WOODBURY[1]

Appeal 2018-007230
Application 14/014,168
Technology Center 1600

Before FRANCISCO C. PRATS, TAWEN CHANG, and DAVID COTTA, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method of detecting a health status in a subject, which have been rejected as obvious, failing to comply with the written description requirement, non-enabling, and being directed to a judicial exception without significantly more. 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 Arizona Board of Regents on behalf of Arizona State University. (Br. 3.)

STATEMENT OF THE CASE

Claims 1, 4, 84, 86–88, and 90 are on appeal.[2] Claim 1 is illustrative and reproduced below:

> 1. (Previously Presented) A method of detecting a health status in a subject, the method comprising:
>
> a) obtaining a dried blood sample;
>
> b) processing the dried blood sample, thereby providing a processed dried blood sample, and obtaining an immunosignature of the sample, comprising;
>
> i) contacting the processed dried blood sample to a peptide array, wherein the peptide array comprises:
>
> a plurality of peptides, each attached to a functionalized surface on at least 10,000 different spots on the array, wherein the peptides are no longer than 20-mers in length and each of the peptides on spots on the array are diverse in peptide structure and sequence space, whereby this construction enhances an off-target binding of antibodies in the processed blood sample to multiple peptides in the array as compared to a solution phase binding of the antibodies in the processed blood sample, wherein the off-target binding comprises multiple binding interactions of the antibodies with various binding strengths to the plurality of peptides in the peptide array,
>
> ii) measuring the off-target binding of the antibodies to the plurality of peptides in the peptide array to form an immunosignature; and

[2] Claims 2, 3, 5–9, 11, 13–83, 85, and 89 have been cancelled. (Br. 18–20 (Claims App.).) Claims 10 and 12 have been withdrawn. (*Id.* at 19.)

iii) detecting the health status of the subject based on the immunosignature, wherein the immunosignature measures changes in binding of the antibodies from the processed blood sample to the peptide array as compared to a-control sera from a plurality of healthy subjects.

(Br. 18 (Claims App.).)

The Examiner rejects claims 1, 4, 84, 86–88, and 90 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. (Ans. 3.)

The Examiner rejects claims 1, 4, 84, 86–88, and 90 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as lacking enablement. (Ans. 8.)

The Examiner rejects claims 1, 4, 84, 86–88, and 90 under 35 U.S.C. § 101 as being directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more. (Ans. 14.)

The Examiner rejects claims 1, 4, 84, 86–88, and 90 under pre-AIA 35 U.S.C. § 103(a) as being unpatenable over Kodadek,[3] Waterboer,[4] and Gao,[5] as evidenced by Lee.[6] (Ans. 20.)

[3] Kodadek, US 2007/0003954 A1, published Jan. 4, 2007.
[4] Tim Waterboer et al., *Dried Blood Spot Samples for Seroepidemiology of Infections with Human Papillomaviruses*, Helicobacter pylori, *Hepatitis C Virus, and JC Virus*, 21 Cancer, Epidemiology, Biomarkers & Prevention 287 (2012).
[5] Gao et al., US 2010/0210478 A1, published Aug. 19, 2010.
[6] Lee et al., US 2005/0255491 A1, published Nov. 17, 2005.

The Examiner rejects claims 1, 4, 84, 86–88, and 90 under pre-AIA 35 U.S.C. § 103(a) as being unpatenable over Andresen,[7] McDade,[8] and Gao, as evidenced by Halperin.[9] (Ans. 20.)

I.

Issue

The Examiner has rejected claims 1, 4, 84, 86–88, and 90 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement.

The Examiner finds that the claims recite a method that detects a health status in a subject but are not limited as to, among other things, the health statuses to be detected, the type of subjects whose health statuses are to be detected, the types of dried blood samples to be used in the method, the methods of obtaining or processing the dried blood samples, the types of immunosignatures obtained, the peptides used in the peptide arrays (other than that the peptides are not longer than 20-mers), the functionalized surfaces used to attach the peptides, the particular antibodies that bind to peptides in the array, the types of off-target binding, or the control sera used. (Ans. 3.)

The Examiner finds that the Specification has not described a representative number of species of the genus encompassed by the claims.

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[7] Heiko Andresen et al., *Deciphering the Antibodyome – Peptide Arrays for Serum Antibody Biomarker Diagnostics*, 6 CURRENT PROTEOMICS 1 (2009).
[8] Thomas W. McDade et al., *What a Drop Can Do: Dried Blood Spots as a Minimally Invasive Method for Integrating Biomarkers into Population-Based Research*, 44 DEMOGRAPHY 899 (2007).
[9] Rebecca F. Halperin et al., *Exploring Antibody Recognition of Sequence Space through Random-Sequence Peptide Microarrays*, 10 MOLECULAR & CELLULAR PROTEOMICS 10.1074/mcp.M110.000786-1 (2011).

(*Id.* at 5.) The Examiner also finds that the Specification does not teach a relevant structure/function relationship for determining which species in the claimed genus of, e.g., dried blood samples, methods of processing, measuring, and detecting, peptide arrays, functionalized surfaces, antibodies, off-target binding activities, immunosignatures, and health statuses would allow the health status in a subject to be detected as recited in the claims. (*Id.* at 8, 29.)

Accordingly, the Examiner finds that the Specification does not reasonably convey to one skilled in the art that Appellants are in possession of the claimed invention. (*Id.*)

Appellants contend that

> the experimental protocols and data submitted with the specification as-filed demonstrate the detection and identification of multiple health statuses simultaneously through immunosignatures, as claimed. *See, e.g.*, Specification at ¶¶ [00161]-[0188]. The disclosure states that the method can be performed in a dried blood sample. *See, e.g.*, *id.* at ¶ [0055]. The exemplary data describe how classification of disease was obtained with high accuracy from both small and large numbers of samples with high accuracy. For instance, 20 samples from each of five different cancer cohorts and 20 noncancer samples (120 total) were used as training/test sets. *Id.*, Table 2. The average accuracy of classification was 0.95. *Id.* at ¶ [00173]. To further investigate the breadth of the approach and test sensitivity to biological diversity, immunosignatures of >1,500 historical samples comprising 14 different diseases were examined by training with 75% of the samples and testing the remaining 25%. *Id.*, Table 3. The average accuracy was >98. A skilled artisan would view these results and reasonably conclude that Appellants had possession of an accurate, simultaneous classification approach for unknown health

> status via the measuring of off-target binding of antibodies to a plurality of peptides in a peptide array, resulting in an informative immunosignature.

(Br. 10–11.)

The issue with respect to this rejection is whether a preponderance of evidence supports the Examiner's finding that the claims fail to comply with the written description requirement.

Analysis

On balance, we find Appellants to have the better argument. The Examiner asserts that

> in Applicant's working examples, no other subjects were used (other than humans); no other substrates were used (other than glass slide); no other peptides were used (other than the ~10,000 or 331,000 specific random peptides synthesized from 18 amino acids that are between 10 and 16 amino acid residues in length); no other samples were used (other than serum, plasma, saliva and venous blood); no other peptide spacing was used (other than 1-2nm apart); no dissociation constants were provided to indicate off-target binding; the most informative peptides are not identified; there are many peptides that bind across different diseases; no other controls were used (other than healthy controls); in one example, the disease signature was noted to buried among the normal variation in antibodies; and there is no example where a dried blood sample was processed or used to produce any immunosignature.

(Ans. 6; *see also id.* at 29.)

The Examiner's focus on the working examples is misplaced. "[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written

description requirement." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc); *see also Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (explaining that "[a] claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language" and that "an actual reduction to practice is not required for written description") (internal quotation marks and citations omitted).

Keeping the above principles in mind, we note that, as to the Examiner's assertion that only humans were used as subjects in Appellants' working examples, the Specification teaches that "[t]he . . . methods of the invention can be used . . . to diagnose, monitor, characterize, and guide treatment of a plurality of different conditions of a subject," wherein "[a] subject can be a human, a guinea pig, a dog, a cat, a horse, a mouse, a rabbit, and various other animals." (Spec. ¶ 142.) The Specification also states that the general approach of "disease determination by immunosignaturing" has been applied to "many chronic diseases in mouse, rat, dog, pig, and human hosts." (Spec. ¶ 85.)

As to the Examiner's assertion that in the working examples "no other substrates were used (other than glass slide)," the Specification states that "[a] surface of peptide array can comprise a plurality of different materials" and can be, for example "glass, functionalized glass, silicon, germanium, gallium arsenide, gallium phosphide, silicon dioxide, sodium oxide, silicon nitrade, nitrocellulose, nylon, polytetrafluoroethylene,

polyvinylidendiflouride, polystyrene, polycarbonate, methacrylates, or combinations thereof." (*Id.* ¶ 115.)

As to the Examiner's assertion that in the working examples "no other peptides were used (other than the ~10,000 or 331,000 specific random peptides synthesized from 18 amino acids that are between 10 and 16 amino acid residues in length)," the Specification discloses general methods of manufacturing arrays comprising predefined, pseudo random, and randomized peptides. (*Id.* ¶¶ 119–131.) The Specification also teaches that,

> [w]hile the sequences of the peptides are entirely random, their off-target captures of antibody are clearly not; rather, the patterns of sera binding to the array are remarkably coherent. An early concern relative to this technology was that the large diversity of antibody species in any serum sample might lead to overlapping binding competitions resulting in a flat, uninformative field of intensities. The data have not borne this out. In fact even a purified monoclonal antibody diluted into serum retains its distinct reactivity pattern with little to no loss of binding.

(Spec. ¶ 81 (citation omitted).)

As to the Examiner's assertions that the working examples used no samples other than serum, plasma, saliva, and venous blood and that there is no example where a dried blood sample was processed or used to produce any immunosignature, the Specification states that a dry blood sample may be used with the claimed methods and further describes how the sample may be collected. (Spec. ¶¶ 55 (describing embodiment wherein fingerstick or fingerprick is used to draw small quantity of blood, which is added to a surface such as filter paper or in a vial and optionally dried), 98 (stating that a dry blood sample on a filter paper may be mailed to a provider of the methods and arrays of the invention).) The Specification teaches that

"[a]ntibodies in blood, plasma, and/or serum can retain their integrity when subjected to . . . drying" and "can retain their integrity when subjected to long term storage either dry, frozen, or desiccated." (*Id.* ¶ 54.) The Specification also teaches a method of processing the dry blood sample. (*Id.* ¶ 91 (explaining that "a dry blood sample . . . is reconstituted in a dilution step prior to being contacted with an array of the invention" and that "a dilution can provide an optimum concentration of an antibody from a biological sample of a subject for immunosignaturing").

As to the Examiner's assertion that in the working examples no peptide spacing was used other than 1–2 nm apart, the Specification teaches that the distance between each peptide in the microarray "can contribute to an off-target binding and/or to an avidity of binding of a molecule to an array" and that this distance can be from about 0.5 nm to 6 nm. (*Id.* ¶¶ 105–108.) The Specification also teaches that

> [t]he high sensitivity [of the microarray technology] is a consequence of the high density of peptides on the slide surface and has been called the "immunosignaturing effect". This has been established by printing and testing different spatial arrangements of peptides on the functionalized glass surface. If arrays are printed such that peptides are spaced about 9 to about 12 nm apart, cognate epitopes compete for antibodies more favorably than the off-target random peptides (with the exception of very strong mimotopes).
>
> We commonly space peptides 1-2 nm apart on average but observe the off-target binding with peptides spaced 3-4 nm apart. If the peptides are spaced from about 1 to about 1.5 nm apart, then an increase in off-target binding is observed. Tightly packed peptides appear to trap antibodies through avidity and rapid rebinding. This

> concept has been shown to be extremely reproducible . . . .

(*Id.* ¶¶ 80–81.)

As to the Examiner's assertion that no controls other than healthy controls were used in the working examples, we note that the claims recite only comparison "to a[]control sera from a plurality of healthy subjects." (Br. 18 (Claims App.).)

The Examiner asserts that "no dissociation constants were provided to indicate off-target binding" in the working examples. (Ans. 6.) In response to Appellants' arguments in the Appeal Brief, the Examiner also asserts that,

> the term "off-target binding" is not defined in the claims or in the instant Specification, and there are no specific binding affinities, targets and/or antibodies recited in the claims that constitute the detection of "off-target binding". Moreover, the claims use the term "comprising" which is open ended and does not exclude additional, unrecited elements or method steps, such that "measuring off-target binding of the antibodies to the plurality of peptides" as recited in claim 1 (ii) also includes, for example, measuring all binding affinities to all antibodies in a sample.

(Ans. 29.)

While we agree that the Specification and the claims do not define "off-target binding" and that "there are no specific binding affinities, targets and/or antibodies recited in the claims that constitute the detection of 'off-target binding,'" it is not clear how this relates to the written description rejection. The Examiner has not rejected the claims based on indefiniteness and has also not suggested that a skilled artisan would not understand the meaning of "off-target binding." Moreover, the Specification suggests that

"off-target binding" is meant to be distinguished from binding to "cognate epitopes." (Spec. ¶ 80.)

We agree that, because the claim uses the transition phrase comprising, "measuring all binding affinities to all antibodies in a sample" would meet the limitation of "measuring off-target binding of the antibodies to the plurality of peptides," *so long as off-target binding occurs when the sample is contacted with the plurality of peptides*. However, we do not understand the relevance of the use of transitional phrase "comprising" to the Examiner's written description rejection. To the extent the Examiner is asserting that the Specification must also provide written description of "measuring all binding affinities to all antibodies in a sample," we are not persuaded. The written description requirement states that the patentee must describe *the invention*, not all elements not specifically excluded from the claim.

As to the Examiner's assertion that no dissociation constants were provided to indicate off-target binding in the working examples, we note that, as discussed above, the Specification teaches that the peptide distance in the microarray "can contribute to an off-target binding and/or to an avidity of binding of a molecule to an array" and that this distance can be from about 0.5 nm to 6 nm. (*Id.* ¶¶ 105–108.) The Specification teaches that "[t]he methods and arrays of the invention can detect[] a broad dynamic range[10] of antibody binding to the peptides in the array of the invention" and that, "[i]n some embodiments, a broad dynamic range of antibody

[10] "A dynamic range of binding of an antibody from a biological sample to a peptide microarray can be described as the ratio between the largest and smallest value of a detected signal of binding." (Spec. ¶ 103.)

binding can be detected on a logarithmic scale." (*Id.* ¶ 103.) The Specification teaches that a molecule can bind to a plurality of peptides in the array with dissociation constants of at least 1 fM to about 100 μM. (Spec. ¶ 102.) The Specification teaches that "[a]n off-target binding, and/or avidity, of a molecule to an array of the invention can, for example, effectively compress binding affinities that span femtomolar (fM) to micromolar (μM) dissociation constants into a range that can be quantitatively measured using only 3 logs of dynamic range." (*Id.* ¶ 101.) The Specification further states that binding interactions can be detected using label-free methods such as surface plasmon resonance (SPR), which can provide a measure of dissociation constants and dissociation rates. (*Id.* ¶ 134.)

The Examiner asserts that "the most informative peptides are not identified" in Appellants' working examples. (Ans. 6.) However, "[t]he descriptive text needed to meet [the written description requirement] varies with the nature and scope of the invention at issue." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). Here, the claims are directed to a general method for detecting health status in a subject based on the changes in binding of the antibodies from the subject's sample to the peptide array comprising at least 10,000 peptides, as *compared* to control sera from healthy subjects. The technology thus does not appear to be dependent on *a priori* knowledge of particular peptide sequences to be incorporated into the array. As discussed above, the Specification also describes methods of manufacturing the peptide arrays of the invention. (Spec. ¶¶ 119–131.) Thus, we are not persuaded that Appellants' failure to identify "the most informative peptides" in the working examples renders written description of

the claimed invention lacking. *See In re Kamal*, 398 F.2d 867, 871 (CCPA 1968) (holding that, despite appellants' concession that "there are many polyfunctional organic compounds containing labile hydrogens that have not been specifically named in appellants' specification," "[t]he fact that appellants' invention is not the . . . compound, per se, but resides instead in the combination of this class of compounds with the novel polyisocyanate makes this extensive disclosure adequate to comply with the section 112 requirements").

Finally, we acknowledge the Examiner's assertion that the Specification notes that "many peptides . . . bind across different diseases" and that, in one example, the disease signature was buried among the normal variation in antibodies. (Ans. 6.) However, the Examiner has not explained how or why these teachings in the Specification show that written description is lacking in light of the rest of the disclosures. For instance, although the Specification teaches that "a number of peptides . . . overlap[ped] at least one other disease when 100 of the most significant T-test peptides for each disease are compared" in a trial to classify different cancers using a method of the invention, which may affect multiple disease classification performance, the Specification also teaches applying a filter to peptides with overlapping specificity and using pattern matching to remove peptides with high signal in more than one disease in order to improve the ability to classify multiple diseases. (Spec. ¶¶ 170–171.)

Likewise, despite the statement in Example 3 that "Panel B shows the consistency across all 10,000 peptides with the disease signature buried among the normal variation in antibodies," the Specification also says in the same example that "[t]he Immunosignaturing binding in pattern in Panel A

indicates a peak prior to the reporting of the symptoms by the subject, followed by a subsequent decline," and that "[t]his demonstrates that a method of the invention can identify an Immunosignaturing binding pattern associated with a condition prior to the appearance of a symptom." (*Id.* ¶ 206.)

In summary, given the disclosures cited above, the Examiner have not persuasively explained why the Specification would not convey with reasonable clarity to those skilled in the art that the inventor was in possession of the claimed method.

The Examiner asserts that prior art references "indicate that not all microarrays comprising all random peptides having any structures and/or all concentrations will function to bind at least one of all antibodies in all samples from all patients, such that all states of health in all patients can be classified." (Ans. 7.) In particular, the Examiner cites:

- Balboni[11] as teaching that, "[a]t the time the invention was made, it was known in the art that given the complex nature of proteins, optimal conditions for antigen arrays have not been established, and variation is seen using different slide surfaces and printing conditions" (*id.* at 6);
- McDade as teaching the potential disadvantages of using dried blood sample in biological assays (*id.* at 6–7);
- Gao[12] as teaching that "it is desirable to develop peptide microarrays that are easy to produce at minimal cost and time

[11] Imelda Balboni et al., *Multiplexed Protein Array Platforms for Analysis of Autoimmune Diseases*, 24 ANN. REV. IMMUNOLOGY 391 (2006).
[12] Gao et al., 8 MOLECULAR DIVERSITY 177 (2004).

consumption, flexible to suit a broad range of needs, specific and sensitive for target detection, capable of large dynamic range of detection, reliable in reproducibility and stable under conditions of assays and storage" (*id.* at 7); and

- Andresen as teaching that "low molecular weight peptides are extremely heterogeneous in their physiochemical properties, such that a uniform unspecific immobilization of peptide probes by simple physiosorption is not feasible beneath a critical peptide length" (*id.*);
- Hilpert[13] as teaching that "a high density of peptides can cause difficulties when assessing the interactions with the molecules of interest, such that the peptide concentration dependency of selected interactions, a reduction in amino group loading may be necessary" (*id.*).

The Examiner asserts that, accordingly,

> the ability to assess *a priori* whether all dried blood samples processed in all ways that are contacted with all arrays of all peptides (having all structures, all lengths as recited, no peptides, all number, synthesized from all molecules etc.) with all processed blood samples, each of the plurality of all peptides attached to all functionalized surfaces, wherein the peptides are no longer than 20-mer in length, wherein all off-target binding comprises all multiple binding interactions of all antibodies in all processed blood samples with all various binding strengths to all of the plurality of peptides in the peptide array; measuring all off-target binding of all antibodies to all of the plurality of all peptides on all peptide arrays to form all immunosignatures, in all combinations, such that all

[13] Kai Hilpert et al., *Cellulose-bound Peptide Arrays: Preparation and Applications*, 24 BIOTECHNOLOGY & GENETIC ENGINEERING REV. 31 (2007).

> health statuses of all subjects (human, fish, dog, rabbit, mice etc.) are detected based on all immunosignatures changes in binding of all antibodies from all processed dried blood samples from all subjects to all peptide arrays as compared to the sera of all controls from all healthy subjects, is not predictable.

(Ans. 7–8.) The Examiner further asserts that "th[e] limited information [provided in the Specification] is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of" the full scope of the claims, because there is no structure/function relationship taught with respect to which species in the claimed genus of samples, peptides, arrays, etc. would allow "all states of health [to] be detected in all subjects," as recited in the claim. (*Id.* at 8.)

We are not persuaded. We agree that the level of detail required to satisfy written description depends on the complexity and predictability of the relevant technology as well as the nature and scope of the claims. *In re Global IP Holdings LLC*, 927 F.3d 1373, 1377 (Fed. Cir. 2019). However, "[i]n addition to predictability, [our reviewing court has also] held that the criticality or importance of an unclaimed limitation to the invention can be relevant to the written description inquiry." *Id.*

In this case, Balboni states that "*optimal* conditions for antigen arrays have not been established, and variation is seen using different slide surfaces and printing conditions." (Balboni 396, right column (emphasis added).) We do not read this statement in Balboni as suggesting that a skilled artisan would find it unpredictable as to whether a peptide array recited in the claims may be made using a variety of surfaces and printing conditions. Indeed, Balboni states that it "evaluated multiple (more than 25) commercially available slide surfaces and assay parameters to optimize

arraying conditions for printing whole antigens and linear peptides." (*Id.*) Moreover, the claim does not rely on the type of surface used in the array or the printing conditions used to distinguish over prior art. *In re Peters*, 723 F.2d 891, 893–94 (Fed. Cir. 1983) (finding tapered tip configuration disclosed in original specification was not critical, and thus did not bar reissue claims to both tapered and nontapered tips, where "[n]o prior art was distinguished from and no rejection was overcome on the basis of the tip shape" and "one skilled in the art would readily understand that in practicing the invention it is unimportant whether the tips are tapered"). Accordingly, we find that the Specification's disclosure relating to the surface of the peptide array to satisfy the written description requirement. (Spec. ¶ 115.)

As to Gao, it is unclear how the Examiner is relying on the statement cited above—which merely expresses generically desirable qualities in a peptide array such as ease of production, low cost/time consumption, flexibility, specificity and sensitivity, large dynamic range detection, reproducibility, and stability—to suggest that the relevant technology is so unpredictable that the disclosures in the Specification fail to convey with reasonable clarity to skilled artisans that the inventors were in possession of a peptide array capable of being used in the claimed method of detecting a health status in a subject.

Similarly, Andresen does state that "[l]ow molecular weight peptides are extremely heterogeneous in their physico-chemical properties" and that, "[f]or this reason, a uniform unspecific immobilization of peptide probes by simply physisorption is not feasible beneath a critical peptide length." (Andresen 2, right column.) The Examiner does not explain, however, why this would call into question whether the inventors were in possession of the

claimed invention, given that the Specification does not appear to require manufacturing the claimed arrays via physisorption of preexisting peptide probes. (Spec. ¶¶ 119–131.) In the same vein, while Hilpert states that "[i]n some cases, a high density of peptides can cause difficulties (e.g., 'ring spot effect' . . .) when assessing the interactions with the molecules of interest" and thus "a reduction in amino group loading may be necessary" (Hilpert 34), the Examiner has not explained whether or how a skilled artisan would understand such difficulties to be applicable to the claimed invention such that a skilled artisan would not understand the inventors to be in possession of the claimed invention despite the disclosures in the Specification.

Finally, as we note in our discussion of the obviousness rejection, *infra*, while McDade does teach potential complications with use of dried blood samples, McDade also teaches that, "[i]n most cases, an analyte that can be measured in serum or plasma can also be assayed in DBS samples" and that, for the most part, "investigators can expect performance that is comparable to that obtained with serum/plasma samples." (McDade 906, 907–908.) Thus, we find that the disclosures in the Specification (*see, e.g.*, Spec. ¶¶ 54–55, 91, 98) regarding collection and processing of dried blood samples convey with reasonable clarity to skilled artisans that the inventors were in possession of a method of using dried blood samples in the claimed method of detecting a health status in a subject.

Accordingly, we reverse the Examiner's rejection of claims 1, 4, 84, 86–88, and 90 as failing to comply with the written description requirement.

II.

Issue

The Examiner has rejected claims 1, 4, 84, 86–88, and 90 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as lacking enablement.

The Examiner asserts that the Specification is enabling for the specific method(s) described in the working examples but is not enabling for the full breadth of the claims. (Ans. 8–10.) The Examiner asserts that the invention "utilizes disciplines of microarray technology, screening, peptide synthesis, and statistical analysis" and that the claimed method is extremely broad because it is not limited as to, e.g., types of dried blood samples or methods of processing them, types of functionalized surfaces for the peptide array, the peptides used for the array (other than that they are no longer than 20-mer in length), or the antibodies or health statuses detected. (*Id.* at 10–11.)

The Examiner asserts that, in contrast, the working samples in the Specification were limited as to the subjects (human), the material for the functionalized surface of the array (glass slide), particular peptides and samples (serum, plasma, saliva and venous blood), peptide spacing (1–2nm), and controls (healthy controls). (Ans. 12.) The Examiner further asserts that the working examples did not provide dissociation constants to indicate off-target binding, did not identify the most informative peptides, showed that there were peptides that bind across different diseases, and showed at least in one example that the disease signature was buried among normal variation in antibodies. (*Id.*)

The Examiner asserts that "[t]he art must . . . be considered to be poorly developed" because "[t]he use of all different and random peptide

arrays that bind to all antibodies in all dried blood samples from all subjects that are processed by all methods for the creation of immunosignatures compared to all controls for the detection of all states of health in all subjects is not highly developed." (Ans. 13.) The Examiner again cites to Balboni, McDade, Gao, Andresen, and Hilpert as indicating that the art is unpredictable and that "not all microarrays comprising all random peptides having any structures and/or all concentrations will function to bind at least one of all antibodies in all samples from all patients, such that all states of health in all patients can be classified." (*Id.* at 13–14.)

Finally, the Examiner asserts that given the unpredictability and the poorly developed state of the art as to

> the use of all peptide arrays (having any number of peptides, all structures, no peptides, all lengths etc.) that bind to all antibodies in all processed dried blood samples from all subjects that are processed by all methods for the creation of all immunosignatures compared to all immunosignatures produced using all control sera for the detection of all states of health in all subjects,

a skilled artisan would have to conduct undue experimentation to practice the claimed invention in light of the lack of working examples and lack of guidance provided by Appellants. (*Id.* at 14.)

Appellants contend that the Specification provides sufficient guidance for a skilled artisan to practice the claimed methods, including

> describing controlled experiments testing an immunosignature system for the diagnosis of cancer and noncancer, including obtaining immunosignatures of >1,500 historical samples comprising 14 different diseases. Specification at ¶¶ [00161]-[0165]. Further, the specification identifies that immunosignatures, such as those of the pending claims, have been applied to more than 33 different diseases and sequelae including viral,

> bacterial, fungal and parasitic infections, cancers, diabetes, autoimmune disease, transplant patients and many chronic diseases in mouse, rat, dog, pig, and human hosts. *Id.* at ¶ [0085]. The specification identifies that peptide microarrays have been available far longer than protein microarrays and cites 17 papers identifying a variety of applications including enzymes, proteins, DNA and small molecules, whole cells, and antibodies. *Id.* at ¶ [0061]. The specification cites eight publications in the field that have used 10,000 unique random-sequence 20-mer peptides to characterize a multitude of disease states. *Id.* at ¶ [0069].

(Br. 11–12.)

The issue with respect to this rejection is whether a preponderance of evidence supports the Examiner's determination that the claims lack enabling disclosure.

Analysis

On balance, we find Appellants to have the better argument.

Claim 1 is broadly drawn to a method of detecting a health status in a subject by contacting a processed dried blood sample to a peptide array having certain characteristics, measuring the off-target binding of the antibodies in the sample to the peptides in the array, and detecting the health status of the subject based on the changes in the binding of the antibodies from the processed blood sample to the array as compared to a control sera from health subjects.

The Specification provides working examples, which the Examiner appears to concede enable at least one or more of the particular methods

used therein. (Ans. 8–9.)[14] Moreover, as discussed above with respect to the written description rejection, the Specification provides guidance for the collection and processing of dried blood samples (Spec. ¶¶ 54, 55, 91, 98); the manufacturing of the peptide array including the types of substrates (*id.* ¶ 115), the peptides (*id.* ¶¶ 119–131) and peptide spacing (¶¶ 80–81, 105–108); and the measurement of off-target binding (¶¶ 101–103, 134). Thus, the Examiner has not established, with evidence, that an undue amount of experimentation would have bene required to make and use the invention.

As we balance the factors relating to enablement, including the broad claim, the presence of working examples, the teachings in the Specification, and the quantity of experimentation required, we conclude that the *Wands* factors do not support the Examiner's conclusion that the claimed invention fails to comply with the enablement requirement.

The Examiner asserts that "not all microarrays comprising all random peptides having any structures and/or all concentrations will function to bind at least one of all antibodies in all samples from all patients, such that all states of health in all patients can be classified." (Ans. 13–14; *see also* Ans.

[14] In response to Appellants' arguments in the Appeal Brief that "the use of random peptide arrays for immunosignaturing regarding a multitude of disease states is well-known in the art," the Examiner asserts that "the immunosignatures of *working examples* are the result of immunosignaturing of all binding affinities, and not solely the off-target binding strengths." (Ans. 30 (emphasis added).) However, enablement takes into consideration the knowledge of a skilled artisan, i.e., what is well-known in the art. Moreover, as discussed above and as the Examiner appears to acknowledge, the claim does not require immunosignatures to be formed *solely* from the off-target binding. Finally, the Examiner has not persuasively explained why, given the way in which the peptide arrays were manufactured in the working examples, the immunosignatures determined in these examples would not be based at least in part on off-target binding.

30–31.) The Examiner points to the Specification as disclosing that some diseases have greater peptide overlap than others, that many peptides have imperfect consistency within a disease, that in one example when a pattern of binding by IgM immunoglobulin to a peptide array is detected and clustered using hierarchical distance, the array failed to organize individual subjects into correct groups, and that "peptides that differ within a cohort but are disease-specific do not negatively impact the specificity for that disease, but can impact sensitivity. (Ans. 30.)

We acknowledge the Examiner's concerns. However, the Examiner has not persuasively explained why the fact peptides may have imperfect consistency within a disease would preclude a skilled artisan from practicing the claimed method without undue experimentation, given that the detection of the health status is based on the immunosignature formed from binding with a plurality of peptides.

In addition, "[i]t is not the function of the claims to exclude inoperable embodiments." *In re Kamal*, 398 F.2d at 870; *Atlas Powder Co. v. E.I. Dupont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984). Of course, if the number of inoperative embodiments becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be nonenabled. However, at least on the record before us, the Examiner has not shown that to be the case.

Accordingly, we reverse the Examiner's rejection of claims 1, 4, 84, 86–88, and 90 as lacking enablement.

III.

Issue

The Examiner has rejected claims 1, 4, 84, 86–88, and 90 under 35 U.S.C. § 101 as being directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

The Examiner concludes that the claims "recite the judicial exception of naturally occurring antibodies in the body of a subject, comparing the measurements obtained to a control and a determination of a health status resulting therefrom, and to the abstract idea of data gathering, data manipulation[,] and data analysis." (Ans. 16.) The Examiner also concludes that the claims are directed to "a general correlation of antibodies that bind to a plurality of different peptides on an array and the determination of a state of health." (*Id.*)

The Examiner finds that "[t]he claims are merely applying a method using well-known, conventional steps without adding a patent eligible application." (*Id.*) The Examiner finds that the independent claims are "recited at a high level of generality, such that substantially all practical applications of the judicial exception related to the antibodies is covered." (*Id.* at 18.) Likewise, the Examiner finds that the dependent claims "[do] not add anything that makes the natural phenomenon in claim 1 significantly different." (*Id.* at 19.) Accordingly, the Examiner finds that the claims as a whole do not recite additional elements that amount to significantly more than the judicial exception itself. (*Id.* at 18–19.)

Appellants contend that the claims are not directed to a patent-ineligible concept and that, to the extent the claims are directed to a patent-

ineligible concept, the claims amount to significantly more than the ineligible concept itself. (Br. 13–14.)

The issue with respect to this rejection is whether the claims are directed to a judicial exception to patentable subject matter (i.e., a law of nature, a natural phenomenon, or an abstract idea), without significantly more.

Analysis

We analyze this case under the framework set forth by the Supreme Court in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012), and applied by our reviewing court in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015). As the *Ariosa* court explained:

> In *Mayo* . . . , the Supreme Court set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to a patent-ineligible concept. . . . If the answer is yes, then we next consider the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application. . . . The Supreme Court has described the second step of this analysis as 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."

Id. at 1375 (alteration in original).

We begin with the first step of the *Mayo* test, namely whether a claim is "directed to" a patent-ineligible concept. On January 7, 2019, the Director of the USPTO issued the "2019 Revised Patent Subject Matter Eligibility Guidance" ("Revised Guidance"), which provides further details regarding how the Patent Office analyzes patent-eligibility questions under 35 U.S.C. § 101. 84 Fed. Reg. 50–57 (Jan. 7, 2019). Under the Revised Guidance, the first step of the *Mayo* test (i.e., Step 2A of the Revised Guidance) is "a two-pronged inquiry." *Id.* at 54. In prong one, we evaluate whether the claim recites a judicial exception, such as laws of nature, natural phenomena, or abstract ideas. *Id.* If the claim recites a judicial exception, the claim is further analyzed under prong two, which requires "evaluat[ion of] whether the claim recites additional elements that integrate the exception into a practical application of that exception." *Id.* The Revised Guidance explains that, "[i]f the recited exception is integrated into a practical application of the exception, then the claim is eligible at Prong Two of . . . Step 2A [of the Revised Guidance]." *Id.*

We find that the claims are not directed to a patent-ineligible judicial exception because, even if the claims recite a judicial exception, the claims also recite additional elements that integrate the exception into a practical application of the exception. As explained in the Revised Guidance, an additional element (or combination of elements) may have integrated a judicial exception into a practical application where the additional element "implements a judicial exception with, or uses a judicial exception in

conjunction with, a particular machine or manufacture that is integral to the claim." 84 Fed. Reg. 55.

In this case, all of the claimed methods of detecting a health status in a subject require contacting a sample to a peptide array having particularly recited characteristics, wherein the health status is based on an immunosignature formed by measuring the off-target binding of the antibodies in the sample to the peptides in the array. Thus, to the extent the claims recite a judicial exception, the claims also include an additional element that implements a judicial exception with, or uses a judicial exception in conjunction with, a manufacture – i.e., the peptide array – that is integral to the claim.

Accordingly, we reverse the Examiner's rejection of claims 1, 4, 84, 86–88, and 90 under 35 U.S.C. § 101 as being directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

IV

Issue

The Examiner has rejected claims 1, 4, 84, 86–88, and 90 under pre-AIA 35 U.S.C. § 103(a) as obvious over Kodadek, Waterboer, and Gao, as evidenced by Lee.

The Examiner finds that Kodadek teaches most of the limitations of claim 1 but concedes that it does not teach using a dried blood sample in its method. (Ans. 20–21, 22.) However, the Examiner finds that Waterboer teaches

> antibody analysis from **dried blood spots** (DBS) on filter paper for **seroepidemiologic infection** and **cancer association** studies, including sexually transmitted

> diseases and screening for newborns, . . . such that quantitative antibody reactivities in serum and DBS show good correlation, where DBS do not require blood centrifugation and allows storage and shipment at ambient temperature, thus, facilitating field work for seroepidemiologic studies, especially in environments with limited technical infrastructure, including the study of . . . human papillomavirus (HPV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and JC polyomavirus (JCV) . . . .

(Ans. 22.)

The Examiner concludes that it would have been prima facie obvious for a skilled artisan at the time of the invention to

> carry out proteomic profiling methods as exemplified by Kodadek using the dried blood spots disclosed by Waterboer . . . with a reasonable expectation of success in creating immunosignature profiles from samples that have been stored and shipped at ambient temperature for seroepidemiologic study, for later processing, and for the analysis of historical samples for the study of diseases, such as cancer and sexually transmitted diseases including HPV, HCV, HIV and JCV.

(*Id.* at 22–23.)

Appellants contend that the cited combination of prior art does not teach using a dried blood sample and in fact teaches away from using such a sample. (Br. 15–16.)

Appellants do not separately argue the claims. Thus, we limit our analysis to claim 1 as representative. The issue with respect to this rejection is whether it would have been obvious to a skilled artisan to use the dried blood sample taught by Waterboer in a method suggested by Kodadek and/or Gao.

Analysis

We agree with the Examiner that claim 1 is obvious over the combination of Kodadek, Waterboer, and Gao, as evidenced by Lee, and address Appellants' arguments below. Only those arguments timely made by Appellants in the Appeal Brief (no Reply Brief was submitted) have been considered; arguments not so presented in the Brief are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

Appellants contend that the cited combination of prior art fails to teach, or teaches away from, using a dried blood sample in a method suggested by Kodadek and/or Gao. In particular,

> [i]n contrast to Kodadek's and Gao's profiling of unknown antibodies, Waterboer tests for antibodies to twelve different specific proteins from four groups of infectious agents, including human papillomaviruses (HPV), Helicobacter pylori (H. *pylori)*, hepatitis C virus (HCV), and JC polyomavirus (JCV). Waterboer requires expressing these known proteins as double fusion proteins with N-terminal glutathione S-transferase and a C-terminal peptide tag as a first step. Waterboer emphasizes the importance of knowing the target antibody in a dried blood sample (DBS) in advance in order to accommodate low antibody levels, stating that "[w]e considered the application of DBS for HPV serology as the main challenge, as because of the absence of systemic infection, natural HPV antibody titers are low."
>
> As such, Waterboer presents a method that fundamentally requires *a priori* knowledge of the protein antigen being analyzed in the dried blood sample. Thus, a skilled artisan would lack a reasonable expectation of

> success in combining Waterboer with Kodadek and/or Gao to arrive at an array wherein peptides on spots on the array are diverse in peptide structure and sequence space, because these structures reflect an array that is used to identify unknown conditions.

(Br. 15–16 (citations omitted).)

We are not persuaded. As an initial matter, Kodadek and Gao do not limit the use of their arrays only to identifications of unknown conditions. Kodadek, for instance, teaches "methods of using . . . ligands . . . that bind ligand binding moieties . . . in complex biological mixtures . . . as biomarkers for a particular physiological state(s)" and further teaches that that "[i]n some cases the identities of ligand binding moieties [are] known prior to the process." (Kodadek ¶ 11.)

Moreover, while the methodology of Waterboer was to test for antibodies to 12 different proteins from four groups of infectious agents, these tests were for the broader purposes of establishing antibody analysis from dried blood spots (DBS) on filter paper for seroepidemiologic infection and cancer association studies. (Waterboer Abstract.) In other words, the specific tests described in Waterboer were intended to validate the use of DBS generally in antibody analysis for seroepidemiologic infection and cancer association studies. Based on these tests, which showed that "[q]uantitative antibody reactivities in serum and DBS showed good correlation," Waterboer concluded that "DBS provide a reliable alternative to serum or plasma for detection of antibodies against various pathogens by multiplex serology." (*Id.*) Appellants have not provided persuasive evidence why, given Waterboer's general conclusion that DBS provides a reliable alternative to serum or plasma for detection of antibodies by multiplex serology, a skilled artisan would not have had reasonable

expectation of success in using DBS to identify disease states in samples, whether or not such diseases states are known or unknown.

Appellants contend that "Waterboer emphasizes the importance of knowing the target antibody in a dried blood sample (DBS) in advance in order to accommodate low antibody levels." (Br. 15.) We are not persuaded. Although Waterboer teaches that correlation between DBS and serum was better for high-titer than for low-titer antibodies (Waterboer 289, right column), Waterboer nevertheless concluded that "DBS provide a reliable alternative to serum samples for seroepidemiologic studies and allow antibody determinations for various pathogens inducing not only high-*but also low-titer* antibody responses" (*Id.* at 293, right column).

In short, we find that Waterboer does not teach away from use of dried blood sample in the methods suggested by Kodadek and/or Gao. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (explaining that a reference may teach away when a skilled artisan, on reading the reference, "would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant"). Neither do we agree that a skilled artisan would not have had a reasonable expectation of success in using the dried blood samples taught by Waterboer in the methods suggested by Kodadek and/or Gao. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[E]xpectation of success need only be reasonable, not absolute."). Accordingly, we affirm the Examiner's rejection of claim 1 as obvious over Kodadek, Waterboer, and Gao, as evidenced by Lee. Claims 4, 84, 86–88, and 90, which are not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

V.

Issue

The Examiner rejects claims 1, 4, 84, 86–88, and 90 under pre-AIA 35 U.S.C. § 103(a) as obvious over Andresen, McDade, and Gao, as evidenced by Halperin.

The Examiner finds that Andresen teaches most of the limitations of claim 1 but concedes that Andresen does not teach using a processed dried blood sample in its method. (Ans. 24–26.) However, the Examiner finds that McDade teaches collecting dried blood spots (DBS) for use in various assays. (*Id.* at 26–27.) The Examiner concludes that a skilled artisan would have had reason to use the dried blood spots taught by McDade in the method described in Andresen, with a reasonable expectation of success, because McDade teaches the benefits of using dried blood spots for biological assays, where such benefits include "easy, low cost collection, transport, and storage of . . . samples." (*Id.* at 28.)

Appellants contend that a skilled artisan would not have had a reasonable expectation of success in using dried blood spot in Andresen's method. (Br. 16.)

Appellants do not separately argue the claims. We therefore limit our analysis to claim 1 as representative. The issue with respect to this rejection is whether a skilled artisan would have had a reasonable expectation of success in using the dried blood spot taught by McDade in the method taught by Andresen.

Analysis

We agree with the Examiner that claim 1 is obvious over the combination of Andresen, McDade, and Gao, as evidenced by Halperin, and

address Appellants' arguments below. Only those arguments timely made by Appellants in the Appeal Brief (no Reply Brief was submitted) have been considered; arguments not so presented in the Brief are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

Appellants contend that

> the Office provides no rationale for why a skilled artisan would have had a reasonable expectation of success in combining Andresen with McDade. Indeed, McDade outlines several disadvantages of using dried blood samples. One of the disadvantages acknowledged by McDade is that assay protocols must be developed specifically for (dried blood samples; "DBS") and validated for accuracy, precision, reliability, and limits of detection." McDade also notes that DBS are "a nonstandard diagnostic substance" and that "the relatively small quantity of sample collected with DBS may also be an insurmountable limitation for some analytes." As such, a skilled artisan would have no reasonable expectation of success in using the hypothetical combination of Andresen and McDade to arrive at the presently claimed method of detecting a health status in a subject.

(Br. 16.)

We are not persuaded. While McDade outlines certain disadvantages of using dried blood spots, it also describes the advantages of using dried blood spots. (McDade 907). As our reviewing court has explained, "a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine." *Medichem, S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). As to Appellants'

contention that a skilled artisan would have no reasonable expectation of success in combining Andresen and McDade to arrive at the claimed invention in light of McDade's description of the disadvantages of using dried blood spots as samples, we note that "the expectation of success need only be reasonable, not absolute." *Pfizer, Inc.*, 480 F.3d at 1364.

We find that the Examiner has established a prima facie case of reasonable expectation of success under the standard set out in *Pfizer*. McDade teaches, for example, that DBS samples have been collected from newborns and evaluated for a number of treatable metabolic disorders for nearly forty years. (McDade 904.) Likewise, McDade teaches that, "[m]ore recently, DBS samples have played central roles in disease-surveillance efforts in several developing countries and have facilitated research on human biology and health in remote settings around the world." (*Id.* at 904.) According to McDade, the CDC has noted that the filter paper collection device, which is used to collect DBS, "has achieved the same level of precision and reproducibility that analytical scientists and clinicians have come to expect from standard methods of collecting blood, such as vacuum tubes and capillary pipettes." (*Id.* (internal quotation marks and citation omitted).)

As to Appellants' contention that McDade acknowledges that "assay protocols must . . . be developed specifically for DBS and validated for accuracy, precision, reliability, and limits of detection," we note McDade states that, for the most part, "this is a relatively methodical process that can take several weeks of dedicated effort." (*Id.* at 907.) Appellants do not persuasively explain why a skilled person would not reasonably expect to be

successful in developing such assay protocols for the methods described in Andresen to arrive at the claimed invention.

Similarly, while McDade notes that DBS is "a nonstandard diagnostic substance," McDade does not suggest that this renders DBS unsuitable for use in diagnostic assays. Rather, McDade explains that while "DBS results may not be directly comparable with those derived from serum or plasma," "correction factors can be applied to DBS values to derive plasma equivalents if desired" because "the correlations between results derived from matched serum/plasma and DBS samples are linear and high for most analytes." (*Id.* at 908.) Appellants have not persuasively explained why, given McDade's explanation that correction factors can be used to render DBS results comparable to results obtained from serum or plasma, a skilled artisan would not have a reasonable expectation of success in using DBS in Andresen's method.

Finally, although Appellants are correct that McDade teaches that "the relatively small quantity of sample collected with DBS may . . . be an insurmountable limitation for some analytes that require large volumes of blood," McDade also teaches that, "[i]n most cases, an analyte that can be measured in serum or plasma can also be assayed in DBS samples"; that, for the most part, "investigators can expect performance that is comparable to that obtained with serum/plasma samples"; and that "[t]he relatively recent development of highly sensitive and specific immunoassays has facilitated analysis of biomarkers in small, microliter quantities of blood." (*Id.* at 906, 908 (emphasis added).) Appellants have not provided persuasive evidence that either the methods described in Andresen or the method of claim 1

requires large volumes of blood for analysis. Andresen, for instance, teaches that

> the site-specific immobilization of peptide probes along with a high local probe density and unrestrained probe accessibility results in the formation of multivalent antibody:peptide complexes and the frequent rebinding of antibodies after complex dissociation. The beneficial outcome of this instance is a high apparent affinity of serum antibodies that correlates with a low detection limit of the immunoassay.

(Andresen 3, right column.) Likewise, while the Specification teaches that in some embodiments of the invention 50 µl of biological samples are required, it also teaches that in other embodiments only about 0.5 nl are required. (Spec. ¶ 90.)

Accordingly, we agree with the Examiner that a skilled artisan would have had a *reasonable* expectation of success in combining Andresen and McDade and affirm the Examiner's rejection of claim 1 as obvious over Andresen, McDade, and Gao, as evidenced by Halperin. Claims 4, 84, 86–88, and 90, which are not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

In summary:

Claim(s) Rejected	Basis	Affirmed	Reversed
1, 4, 84, 86–88, and 90	§ 112 Written Description		1, 4, 84, 86–88, and 90
1, 4, 84, 86–88, and 90	§ 112 Enablement		1, 4, 84, 86–88, and 90
1, 4, 84, 86–88, and 90	§ 101 Ineligible Subject Matter		1, 4, 84, 86–88, and 90
1, 4, 84, 86–88, and 90	§ 103 Kodadek, Waterboer, Gao, and Lee	1, 4, 84, 86–88, and 90	
1, 4, 84, 86–88, and 90	§ 103 Andresen, McDade, Gao, and Halperin	1, 4, 84, 86–88, and 90	
Overall Outcome		1, 4, 84, 86–88, and 90	

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)(i)(iv).

AFFIRMED