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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte LENNART BJORKESTEN, SOFIA EDLUND, and ASA HAGNER-MCWHIRTER

Appeal 2018-007155
Application 14/128,379
Technology Center 1600

Before DONALD E. ADAMS, ERIC B. GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134(a) involving claims to a method for identification of specific target biomolecules in a sample in a detection procedure. The Examiner rejected the claims as obvious and as reciting non-statutory subject matter. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as GE Healthcare Bio-Sciences AB (*see* Appeal Br. 2).

Statement of the Case

Background

Western blotting is an analytic technique that "uses gel electrophoresis to separate native or denatured proteins by the length of the polypeptide . . . or by the 3-D structure of the protein . . . [t]he proteins are then transferred to a membrane . . . where they are probed (detected) using antibodies specific to the target protein" (Spec. 1:11–17)

> Due to possibilities of increased signal amplification and to avoid negative effects on target specific affinity related to primary antibody conjugation, [the membrane probing] traditionally takes place in a two-step process (using a primary target specific antibody and a secondary labeled antibody specific for the primary antibody), although there are now one-step detection methods available for certain applications.

(*Id.* 1:22–26). The one-step method "allows the process to occur faster" but "requires a probe antibody which both recognizes the protein of interest and contains a detectable label" (*id.* 1:27–29).

"The present invention uses several probes, preferably antibodies, directed against the same or different epitopes of the same target protein. These antibodies may be more or less specific. Since the method of the invention combines the signals from the different antibodies, specific signal can be discriminated from unspecific ones" (Spec. 4:26–29).

The Claims

Claims 1, 3, 4, 9–19, 21, 22, and 24–28 are on appeal. Independent claim 1 is representative and reads as follows:

> 1. A method for identification of specific target biomolecules in a sample in a detection procedure, comprising:

> probing a gel or membrane with at least two probes that are directed against and specifically bind to a same target biomolecule to form bands or spot patterns on the gel or membrane;
>
> obtaining image sample patterns corresponding to the bands or spot patterns;
>
> overlaying the image sample patterns with each other;
>
> generating image data by applying an algorithm that uses pixel-wise multiplication to enhance overlapping features and diminish non-overlapping features of the bands or spot patterns in the overlayed image sample patterns;
>
> scaling the image data using a root function; and
>
> differentiating the bands or spot patterns corresponding to specific binding of the probes to the target biomolecule in the sample from non-specific binding of the probes to other biomolecules in the sample using the scaled image data.

Appeal Br. 18.

The Issues

A. The Examiner rejected claims 1, 3, 4, 9, 10, 13, 19, 21, 22, and 26 under 35 U.S.C. § 103(a) as obvious over Leimgruber[2] and Morris[3] (Ans. 6–9).

B. The Examiner rejected claims 11 and 12 under 35 U.S.C. § 103 as obvious over Leimgruber, Morris, and Berth[4] (Ans. 9–10).

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[2] Leimgruber et al., *Development of improved cell lysis, solubilization and imaging approaches for proteomic analyses*, 2 Proteomics 135–44 (2002).
[3] Morris et al., US 2008/0166030 A1, published July 10, 2008.
[4] Berth et al., *The state of the art in the analysis of two-dimensional gel electrophoresis images*, 76 Appl. Microbiol. Biotechnol. 1223–43 (2007).

C. The Examiner rejected claims 14, 16, 17, and 28 under 35 U.S.C. § 103 as obvious over Leimgruber, Morris, and Tacha[5] (Ans. 10–11).

D. The Examiner rejected claim 15 under 35 U.S.C. § 103 as obvious over Leimgruber, Morris, and Uhlen[6] (Ans. 11).

E. The Examiner rejected claim 18 under 35 U.S.C. § 103 as obvious over Leimgruber, Morris, Tacha, and Uhlen (Ans. 11–12).

F. The Examiner rejected claim 24 under 35 U.S.C. § 103 as obvious over Leimgruber, Morris, Tacha, and Czerney[7] (Ans. 12–13).

G. The Examiner rejected claim 25 under 35 U.S.C. § 103 as obvious over Leimgruber, Morris, and Pieper[8] (Ans. 13–14).

H. The Examiner rejected claim 27 under 35 U.S.C. § 103 as obvious over Leimgruber, Morris, and Bio-rad[9] (Ans. 14–15).

I. The Examiner rejected claims 1, 3, 4, 9–19, 21, 22, and 24–28 under 35 U.S.C. § 101 as directed to a judicial exception (Ans. 3–5).

A. 35 U.S.C. § 103(a) over Leimgruber and Morris

The Examiner finds that Leimgruber teaches a

> method for identification of a specific target biomolecule[] (protein) in a sample in a detection procedure (Gel Blot overlay Approach described in Fig. 2) comprising: probing a gel with a least two probes (various anti-phosphorylation antibodies such as antibodies to phosphoserine, phosphothreonine, phosphotyrosine, phosphoMAPKs, and phospho-hsp27) that are directed against and specifically bind to a same target

[5] Tacha, US 2005/0186642 A1, published Aug. 25, 2005.
[6] Uhlen et al., US 2008/0233660 A1, published Sept. 25, 2008.
[7] Czerney et al., US 7,745,640 B2, issued June 29, 2010.
[8] Pieper et al., US 7,642,089 B2, issued Jan. 5, 2010.
[9] Quantity One, User Guide for Version 4.2.1, Bio-Rad Laboratories (2000) ("Bio-rad").

> biomolecule (phosphorylated protein) to form bands or spot patterns on the gel or membrane (the spots are formed by the labels which bind to the antibodies.

(Ans. 6–7). The Examiner acknowledges that "Leimgruber does not teach the generating, scaling, or differentiating steps" (*id.* at 7).

The Examiner finds Morris teaches "enhancing overlapping features and sorting out nonoverlapping features of the bands or spot patterns in the overlaid sample patterns to generate image data by creating an average gel image, which averages out noise (diminishes nonoverlapping features) and reinforces real protein spots" (Ans. 7). The Examiner finds it obvious to combine these teachings "because Leimgruber teaches using image processing and Morris teaches methods of processing data overlays of gels which differentiate specific protein binding" (Ans. 7–8).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that Leimgruber and Morris render the claims obvious?

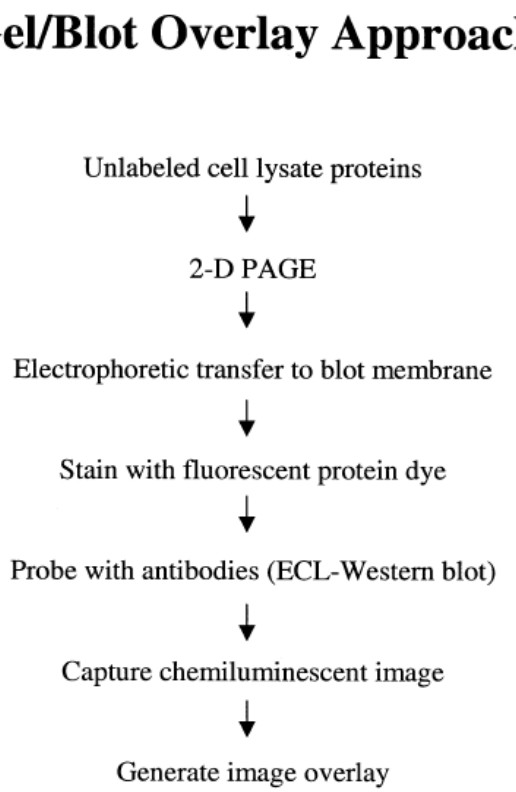
Findings of Fact

1. Leimgruber teaches a biomolecule detection method in which

> proteins are transferred from two-dimensional (2-D) gels to blot membranes. Proteins are then detected by staining with SYPRO Ruby and the resulting 2-D protein pattern is captured using a charge-coupled device (CCD) camera. The blots are then probed with antibodies directed against the protein(s) or functionalities of interest. The resulting chemiluminescent blot image is also generated with the CCD camera and the fluorescent SYPRO Ruby image is recaptured again without moving the membrane. It is thereby possible to generate a direct image overlay of the blot pattern on that of the stained protein pattern.

(Leimgruber 135, abstract).

2. Figure 2 of Leimgruber is reproduced below:



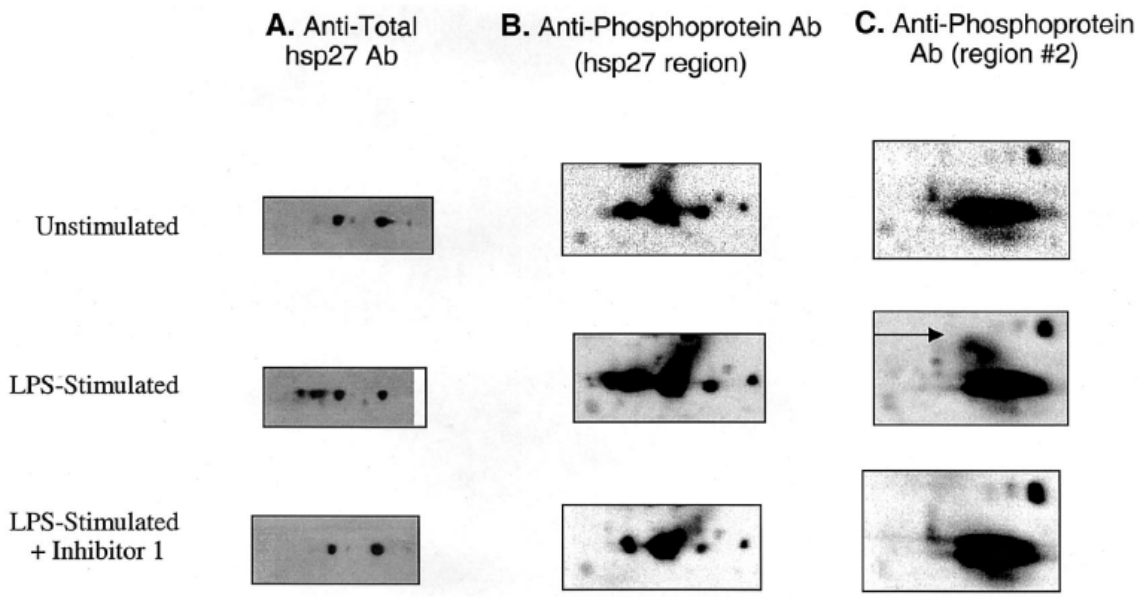
"Figure 2. Gel/blot overlay approach. A schematic of the chemiluminescent Western blot image overlay on the fluorescent protein stain" (Leimgruber 139, col. 1).

3. Leimgruber teaches:

> The anti-hsp27 antibody was obtained from Santa Cruz (Santa Cruz, CA, USA) and the antiphosphoprotein antibodies were from Zymed (San Francisco, CA, USA), Upstate Biochemicals (Lake Placid, NY, USA) and Cell Signaling Technologies (Beverly, MA, USA) (mixtures of antibodies to phosphoserine, phosphothreonine, phosphotyrosine, phospho-MAPKs, phospho-hsp27).

(Leimgruber 137, col. 1).

4. Figure 5 of Leimgruber is reproduced below:



"**Figure 5**. Effects of inhibitor treatment on the phosphorylation of hsp27 and an unknown protein. U937 treatments are indicated for each row and the antibodies used for protein detection are indicated at the top of each column" (Leimgruber 141).

5. Morris teaches

> a method and computer program product for detecting and quantifying protein spots, including: generating an average gel image by taking a pixel-by-pixel average of the intensities of a plurality of aligned gel images; detecting spots on the average gel image using pinnacle detection; and quantifying spots on individual gels using the maximum intensity within fixed neighborhoods surrounding pinnacle locations found in the average gel image.

(Morris, abstract; *see* Morris ¶ 23).

Principles of Law

"Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set

of circumstances is not sufficient." *MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

Analysis

Appellant contends "the Examiner provides no evidence that any two of the phosphoserine, phosphothreonine, phosphotyrosine, phospho-MAPKs, and phospho-hsp27 antibodies specifically bind to a same biomolecular species, and therefore has not made a *prima facie* case showing that Leimgruber teaches Appellant's claimed at least two probes" (Appeal Br. 13).

The Examiner responds that Leimgruber "provides evidence that the anti-phosphorylated antibodies bind to hsp-27, thereby providing evidence that both probes (i.e. at least two of the antibodies to phosphoserine, phosphothreonine, phosphotyrosine, phosphoMAPKs, and phospho-hsp27) bind to the same target" (Ans. 21–22). The Examiner finds "based on this evidence, it is likely that the antibodies to phospho-hsp27 and at least one of the antibodies to phosphoserine, phosphothreonine, and phosphotyrosine bind to hsp-27, thereby indicating two probes are able to bind to the same phosphorylated protein" (*id.* at 22).

We agree with Appellant because the Examiner is not arguing that it would have been obvious to use two antibodies to the same target protein but rather is arguing that Leimgruber's assay teaches antibodies that inherently do so. However, the Examiner expressly states that Leimgruber's antibodies "likely" bind the same target protein, not that these antibodies *necessarily* bind the same target protein. The rejection therefore does not apply the correct requirement for an inherency teaching. Inherency does not require that the missing descriptive material be present "more likely than not," but

rather that it "is 'necessarily present.'" *Trintec Indus., Inc. v. Top-U.S.A. Corp*., 295 F.3d 1292, 1295 (Fed. Cir. 2002) (*quoting In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). More specifically, under the principles of inherency, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *See In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). Because there is no evidence that the antibodies of Leimgruber necessarily bind the same target protein, and consequently no evidence of inherency, and the Examiner has not provided a reasoned basis for modifying Leimgruber's method to include such antibodies, there is no prima facie case of obviousness.

Conclusion of Law

A preponderance of the evidence of record does not support the Examiner's conclusion that Leimgruber and Morris render the claims obvious.

B.–H. 35 U.S.C. § 103

The Examiner does not rely upon any of the additional cited references to teach two antibodies binding to the same target protein (*see* Ans. 9–15), but rather relies upon these references to address elements of the dependent claims. Having reversed the obviousness rejection of claim 1 for failing to necessarily teach the use of two antibodies to the same target protein for the reasons given above, we also find that the further combinations do not address this issue and therefore do not render the rejected claims obvious for the same reasons.

I. 35 U.S.C. § 101

The Examiner finds the claims "directed to a method for identification of specific target biomolecules in a sample in a detection procedure" but are "directed to an abstract idea, because all steps except for probing are mere data manipulation and data analysis" (Ans. 3–4). The Examiner finds the "additional elements (the probing and obtaining steps) are nothing more than routine generic measurement steps using two probes against an analyte on a gel or membrane and obtaining an image" (*id.* at 4).

Appellant contends the "focus of the claims, when read in light of the specification, is on a particular method for increasing the specificity of target protein identification in protein immunoblots and quantitative comparisons" (Appeal Br. 6). Appellant contends the inventors "discovered a particular solution to this problem—using two probes directed against the same or different epitopes of a target biomolecule to obtain signals which are then processed according to a specific sequence of steps that enhances signals from the true target biomolecule" (*id.* at 7).

Appellant also contends the Examiner did not "establish or provide any rational explanation as to why the claimed subject matter as a whole (e.g., as an ordered combination) is routine and conventional activity and does not amount to significantly more than the alleged judicial exceptions of data manipulation, mathematical steps, and data analysis" (Appeal Br. 10).

Principles of Law

An invention is patent-eligible if it claims a "new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101. However, the Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit exceptions: "[l]aws of nature, natural phenomena, and abstract

ideas" are not patentable. *See, e.g.*, *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014).

In determining whether a claim falls within an excluded category, we are guided by the Supreme Court's two-step framework, described in *Mayo* and *Alice*. *Id.* at 217–18 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 75–77 (2012)). In accordance with that framework, we first determine what concept the claim is "directed to." *See Alice*, 573 U.S. at 219.

If the claim is "directed to" an abstract idea, we turn to the second step of the *Alice* and *Mayo* framework, where "we must examine the elements of the claim to determine whether it contains an 'inventive concept' sufficient to 'transform' the claimed abstract idea into a patent-eligible application." *Alice*, 573 U.S. at 221 (quotation marks omitted). "A claim that recites an abstract idea must include 'additional features' to ensure 'that the [claim] is more than a drafting effort designed to monopolize the [abstract idea].'" *Id.* (quoting *Mayo*, 566 U.S. at 77). "[M]erely requir[ing] generic computer implementation[] fail[s] to transform that abstract idea into a patent-eligible invention." *Id.*

The United States Patent and Trademark Office published guidance on the application of 35 U.S.C. § 101. USPTO's *2019 Revised Patent Subject Matter Eligibility Guidance* ("Guidance").[10] Under the Guidance, in determining what concept the claim is "directed to," we first look to whether the claim recites:

> (1) any judicial exceptions, including certain groupings of abstract ideas (i.e., mathematical concepts, certain methods

[10] *2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50–57 (January 7, 2019).

> of organizing human activity such as a fundamental economic practice, or mental processes) (Guidance Step 2A, Prong 1); and
>
> (2) additional elements that integrate the judicial exception into a practical application (*see* MPEP §§ 2106.05(a)–(c), (e)–(h)) (Guidance Step 2A, Prong 2).

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

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

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

Analysis

Applying the Revised Guidance to the facts on this record, we find that Appellant's claims 1, 3, 4, 9–19, 21, 22, and 24–28 are directed to patent-eligible subject matter. Because the same issues are present in each of the claims, we focus our consideration on representative claim 1. The same analysis applied below to claim 1 also applies to the other rejected claims.

A. Guidance Step 1

We consider whether the claimed subject matter falls within the four statutory categories set forth in § 101, namely "[p]rocess, machine,

manufacture, or composition of matter." 2019 Guidance 53–54; *see* 35 U.S.C. § 101. Claim 1 recites a "method" thus, fall within the "process," category. Consequently, we proceed to the next step of the analysis.

B. Guidance Step 2A, Prong 1

The Revised Guidance instructs us first to determine whether any judicial exception to patent eligibility is recited in the claim. The Revised Guidance identifies three judicially-excepted groupings identified by the courts as abstract ideas: (1) mathematical concepts, (2) certain methods of organizing human behavior such as fundamental economic practices, and (3) mental processes.

Claim 1 recites limitations that reasonably fall within the "mathematical concept" grouping listed in the Revised Guidance. "[C]laims focused on 'collecting information, analyzing it, and displaying certain results of the collection and analysis' are directed to an abstract idea." *SAP America, Inc. v. InvestPic, LLC,* 898 F.3d 1161, 1167 (Fed. Cir. 2018). Here, claim 1 collects image pattern data, analyzes that data with an algorithm and scales the data using a root function, and then uses the data to differentiate band or spot patterns. The Specification teaches:

> A more detailed example of an algorithm for the purpose described above for two antibodies is:
>
> **$P_t(n) = SQRT(P_1(n) . P_2(n))$** where
>
> **$P_t(n)$** is the signal intensity in an image pixel (n) representing the target protein Western pattern.
>
> **$P_1(n)$** is corresponding value from an image representing the Western pattern from the first Ab.
>
> **$P_2(n)$** is corresponding value from an image representing the Western pattern from the second Ab.

(Spec. 5:11–19). While we recognize claim 1 is limited to protein analysis, "even if a process of collecting and analyzing information is 'limited to particular content' or a particular 'source,' that limitation does not make the collection and analysis other than abstract." *SAP*, 898 F.3d at 1168.

C. Guidance Step 2A, Prong 2

Having determined that the claims recite a judicial exception, the Revised Guidance directs us to next consider whether the claims integrate the judicial exception into a practical application. Guidance Step 2A, Prong 2. "[I]ntegration into a practical application" requires that the claim recite an additional element or a combination of elements, that when considered individually or in combination, "apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception." Guidance at 54.

A judicial exception is not integrated into a practical application when the claims are drawn to the mere use of "a computer as a tool to perform an abstract idea." Guidance, 84 Fed. Reg. at 55.

Here, claim 1 is more similar to those held ineligible in *Mayo* than they are to those held eligible in *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd*., 887 F.3d 1117 (Fed. Cir. 2018) because claim 1 lacks a step that recites more than the use of the algorithm like the claims in *Vanda* which "recite more than the natural relationship between CYP2D6 metabolizer genotype and the risk of QTc prolongation. Instead, they recite a method of treating patients based on this relationship that makes iloperidone safer by lowering the risk of QTc prolongation." *Vanda*, 887 F.3d at 1136.

Therefore claim 1 does not recite elements that integrate the abstract idea into a practical application that is more than the abstract idea itself.

D. Guidance Step 2B

Having determined that the judicial exception is not integrated into a practical application, the Revised Guidance requires us to evaluate the additional elements individually and in combination to determine whether they provide an inventive concept, such as a specific limitation beyond the judicial exception that is not well-understood, routine, conventional in the field, or simply appends well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception. *See* 84 Fed. Reg. 51.

Berkheimer mandates evidence showing the claim elements were well-understood, routine, and conventional in the prior art is necessary to satisfy *Alice* step two. *See Berkheimer v. HP Inc*., 881 F.3d 1360, 1369 (Fed. Cir. 2018) (noting that "[whether] something is well-understood, routine, and conventional to a skilled artisan at the time of the patent is a factual determination.").

Appellant contends the Examiner "failed to establish or provide any rational explanation as to why the claimed subject matter as a whole (e.g., as an ordered combination) is routine and conventional activity and does not amount to significantly more than the alleged judicial exceptions of data manipulation, mathematical steps, and data analysis" (Appeal Br. 10).

The Examiner responds "as explained in the Non-Final rejection at 16, the references in the 103(a) rejection show that using two probes and obtaining an image (the additional elements in combination) are routine and

conventional and therefore the claims are not significantly more than the abstract idea" (Ans. 20).

In this case, the Examiner has provided no evidence that the central step in the method of claim 1, "probing a gel or membrane with at least two probes that are directed against and specifically bind to a same target biomolecule", was known in the prior art. As discussed in our analysis above of the obviousness rejection, Leimgruber and the other cited prior art do not disclose or demonstrate an assay where two different probes are used that necessarily bind to the same target biomolecule in a sample, whether in a Western blotting procedure or other procedure. Moreover, even if it were accidentally inherent in Leimgruber that two different antibodies did bind a single target biomolecule, it is unclear if that would be sufficient to establish that such a use of multiple antibodies on a single protein is routine and conventional.

Moreover, the Examiner provides no other evidence that such an assay is well known, routine, or conventional. It is the Examiner's burden to establish, for the purposes of this rejection, that the elements of the claims were routine and conventional. *See* MPEP § 1213.02 ("The Board's primary role is to review the adverse decision as presented by the Examiner, and not to conduct its own separate examination of the claims.").

The rejection of the claims under 35 U.S.C. § 101 is reversed.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 3, 4, 9, 10, 13, 19–22, 26	103	Leimgruber, Morris		1, 3, 4, 9, 10, 13, 19–22, 26
11, 12	103	Leimgruber, Morris, Berth		11, 12
14, 16, 17, 28	103	Leimgruber, Morris, Tacha		14, 16, 17, 28
15	103	Leimgruber, Morris, Uhlen		15
18	103	Leimgruber, Morris, Tacha, Uhlen		18
24	103	Leimgruber, Morris, Tacha, Czerney		24
25	103	Leimgruber, Morris, Pieper		25
27	103	Leimgruber, Morris, Bio-rad		27
1, 3, 4, 9–19, 21, 22, 24–28	101			1, 3, 4, 9–19, 21, 22, 24–28
Overall Outcome				1, 3, 4, 9–19, 21, 22, 24–28

REVERSED