

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte STEVEN M.C. CHAN and PAUL J. UTZ

Appeal 2008-0305
Application 11/040,736
Technology Center 1600

Decided: February 29, 2008

Before TONI R. SCHEINER, DONALD E. ADAMS, and ERIC GRIMES,
Administrative Patent Judges.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods for the microarray analysis of post-translational modifications of proteins. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

“Microarrays offer an attractive and convenient platform for multiplex protein analysis” (Spec. 1). Reverse phase protein (RPP) microarrays “are constructed by depositing small volumes of cell lysates onto a high protein-binding substratum using a robotic microarrayer. Each cell lysate microspot

contains the full complement of intracellular proteins,” and the “arrays are then probed with antibodies, and the signal intensity of each microspot correlates with the level of the analyte. Since thousands of samples can be spotted in high density onto a single slide, a large number of samples can be monitored simultaneously” (*id.*).

The Specification discloses methods for “a multiplexed reverse phase protein (RPP) microarray platform, which is utilized for simultaneous monitoring of cellular components” wherein components affected by post-translational modification are of particular interest (*id.* at 2).

DISCUSSION

1. CLAIMS

Claims 1-4, 8, and 12 are pending and on appeal. Claim 1 is representative and reads as follows:

Claim 1: A method of determining a pattern of response to an agent, the method comprising:

- contacting a plurality of different cells with an agent;
- preparing whole cell lysates of each of said different cells;
- immobilizing each of said whole cell lysates on a microarray;
- preparing whole cell lysates of a said plurality of different cells in the absence of contacting with said agent; and
- immobilizing said whole cell lysates on said microarray;
- probing said whole cell lysates on said microarray with a reagent that specifically recognizes a post-translational modification of a polypeptide of interest; and
- determining the alteration in post-translational modification as a result of said contacting with said agent.

2. OBVIOUSNESS I

Claims 1-4, 8, and 12 stand rejected under 35 U.S.C. § 103 as obvious in view of Espina¹ and Shen.² Claims 2-4, 8, and 12 have not been argued separately and therefore stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner relies on Espina as disclosing “reverse phase protein microarrays for gathering information about the post-translational modifications of proteins” and that “the post-translational modifications ... can be profiled by ... monitoring the total and phosphorylated proteins over time, before and after treatment” (Answer 4).

The Examiner further finds that Espina “differs from the instant invention in failing to specifically state contacting the cells with an agent” (*id.*). The Examiner relies on Shen as disclosing “determining post-translation modification of a protein ... by using antibodies which bind specifically to the immobilized protein which has been modified” and “comparing untreated and treated cells using an array,” wherein “the treatment can be with drugs (pharmaceutical agent)” (*id.* at 5).

The Examiner concludes that it “would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate drugs as taught by Shen et al. for the treatment as taught by Espina et al. because Espina et al. teaches that the samples can be obtained before and after treatment and Shen et al. teaches that treatment with drugs provides for

¹ Espina et al., *Proteomics* 3:2091-2100 (2003).

² Shen et al., US 2003/0153014, Aug. 14, 2003.

a comparison to monitor the activation state of signal pathways and determining post-translational modification” (*id.*).

We conclude that the Examiner has set forth a prima facie case that claim 1 would have been obvious to the ordinary artisan. Espina discloses protein microarrays to study the post-translational modifications of proteins and teaches that a “subclass of protein microarrays, Reverse Phase Arrays ... has been optimized for use with tissue specimens” (Espina, abstract). Espina also discloses “[m]onitoring the total and phosphorylated proteins over time, before and after treatment” (*id.* at 2092) by probing the arrays “separately with two different classes of antibodies to specifically detect the total and phosphorylated forms of the protein” (*id.*). Espina also discloses that “array formats consist of multiple patients on a single array, often representing samples obtained before and after treatment ..., allowing comparison of analytes across samples on an array” (*id.* at 2095).

Shen discloses a sandwich immunoassay for the detection of post-translationally-modified proteins (Shen, abstract and Fig. 1) and that “bound target proteins are ... contacted with detection molecules specific for the subject protein modification” (*id.* at para. 0124). Shen also discloses that “[w]here a comparison is made using a protein array, e.g. a comparison between a control array and an array from a protein mixture of a particular condition or change in a condition, the control sample can be . . . , e.g. untreated cells and the experimental sample can be treated cells” (*id.* at para. 0134). Shen also discloses that the “treatment can be ... any drug treatment whether a known approved drug or a test drug” (*id.*).

We agree with the Examiner that it would have been *prima facie* obvious to a person of ordinary skill in the art to combine the teachings of Espina and Shen and thereby arrive at the method of claim 1. Espina teaches reverse phase protein microarrays to profile post-translational modifications of proteins using samples before and after treatment. Shen teaches both test arrays and control arrays to evaluate post-translational modification of proteins, using untreated cells as control samples and treated cells as experimental samples, and where the treated cells are treated with agents (i.e. drugs).

The Espina disclosure on protein microarrays to study post-translational modification and the Shen teaching to combine a control array and a test array in the analysis of protein post-translational modification would have suggested the instantly claimed invention because one of ordinary skill in the art would have recognized that it would be more efficient to analyze treated and untreated samples (i.e. a control array) on the same array. *See Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1368 (Fed. Cir. 2006):

[A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the ‘improvement’ is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. . . . In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him *capable* of combining the prior art references.

Appellants argue that a prima facie case of obviousness has not been established because “the recited combination fails to teach all the elements of the rejected claims” (Appeal Br. 6). Specifically, Appellants argue that

although Espina presents a general review of the use of reverse phase protein arrays for the analysis of whole cell lysates, Espina does not teach or suggest the step of contacting a plurality of different cells with an agent prior to preparing ... and immobilizing the whole cell lysates on a microarray. Accordingly, the microarray of immobilized whole cell lysates disclosed in Espina include[s] only whole cell lysates that have been prepared in the absence of contacting with an agent.”

(*Id.*) Appellants also argue that “Shen fails to remedy the deficiencies of Espina because Shen does not teach or suggest a single microarray that includes both a whole cell lysate that has been contacted with an agent and . . . a whole cell lysate that is immobilized on the microarray without having been contacted with the agent” (*id.*).

We do not find this argument to be persuasive. While neither Espina nor Shen expressly suggests a single array containing lysates from both control and treated cells, the prior art need not expressly suggest an invention in order to have made it obvious. “[T]he ‘motivation-suggestion-teaching’ test asks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims.” *In re Kahn*, 441 F. 3d 977, 988 (Fed. Cir. 2006). *See also KSR Int’l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (The obviousness analysis “can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.”); *Dystar*, 464 F.3d at 1367 (The

“suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense.”).

Here, Espina discloses protein arrays to evaluate both treated and untreated samples and Shen discloses both test and control arrays (i.e. antibody arrays for protein analysis). One of skill in the art would have considered the combined teachings of Espina and Shen to suggest the disputed limitation, i.e. having protein lysates from both control and treated samples on the same array, since such an arrangement would improve the efficiency of analyzing post-translational modifications.

Appellants further argue that there is no motivation to combine the references because Espina’s teaching “that samples can be obtained before or after treatment” is not specifically cited by the Examiner and because the Examiner does not “cite to where, in either reference, there is a teaching or suggestion of obtaining samples before and after treatment and immobilizing those samples on a single microarray,” and thus a motivation has not been shown in the references or in the art to combine the specific elements of Espina with Shen to derive the claimed invention (Appeal Br. 7).

We do not find this argument to be persuasive. “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 127 S.Ct. at 1739. “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the relevant question is “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 1740. Espina discloses protein arrays for the analysis of protein post-translational modification, including cellular

samples before and after treatment and the use of antibodies specific for modified proteins, and Shen discloses the use of test arrays and control arrays in monitoring post-translational modification of proteins. The combination of Espina's protein arrays with Shen's control samples and test samples appears to be nothing more than the combination of old elements to yield predictable results.

3. OBVIOUSNESS II

Claims 1-4, 8, and 12 stand rejected under 35 U.S.C. § 103 as obvious in view of Charboneau³ and Shen. Claims 2-4, 8, and 12 have not been argued separately and therefore stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner relies on Charboneau as disclosing reverse phase protein microarrays formed from cell lysates that are immobilized on the microarray, to investigate signal transduction pathways (Answer 5). The Examiner finds that Charboneau discloses forming lysates from cells that have been treated with agents and from cells that have not been treated with the agent (*id.* at 5-6). The Examiner also finds that Charboneau discloses "probing the microarray with antibodies which are specific for the target protein" and "monitoring the activation status of proteins" (*id.* at 6).

The Examiner finds that Charboneau "differs from the instant invention in failing to specifically teach determining a post-translation modification of a polypeptide of interest" (*id.*). The Examiner relies on Shen as disclosing that the post-translational modification of a protein can be

³ Charboneau et al., Briefings in Functional Genomics & Proteomics 1(3):305-315 (2002).

determined and that this modification can be probed by “using antibodies which bind specifically to the immobilized protein which has been modified” (*id.*). The Examiner further finds that Shen discloses “treating cells with agents such as drugs and chemicals and testing to determine the protein modification” (*id.*).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Shen’s detection of post-translational modifications with Charboneau’s method because Charboneau teaches that “signal pathway and protein modification analysis can be done on any cell type” and Shen teaches antibodies for detecting post-translational modifications and specific target proteins for signal pathway analysis (*id.*).

We conclude that the Examiner has set forth a prima facie case that claim 1 would have been obvious to the ordinary artisan. Charboneau discloses that reverse phase protein microarrays “constitute a sensitive high throughput platform for marker screening” (Charboneau abstract).

Charboneau also discloses that pure protein lysates can be “isolated either from tissue or cultured cells” and that “[o]ver 1,000 individual cellular lysates can be accommodated on a 20 X 50 mm slide” (*id.* at 307).

Charboneau also discloses that reverse phase protein microarrays “allow the monitoring of the relative activation status of proteins as a function of . . . treatment” (*id.* at 309). Shen’s disclosure is discussed above.

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of Charboneau and Shen and thereby arrive at the

method of claim 1. Charboneau discloses protein microarrays for high throughput analysis of multiple protein lysates, and the use of such microarrays to monitor protein changes caused by treating cells with an agent. Shen teaches both test and control arrays to evaluate protein post-translational modification, using modification-specific agents, using control samples (untreated cells) and experimental samples (cells treated with a variety of agents). One of skill in the art would have been motivated to combine control and test samples on the same array in the analysis of protein post-translational modification because it would be more efficient than using separate arrays for treated and untreated samples.

Appellants argue that a prima facie case of obviousness has not been established because there is no motivation to combine the references and because the Examiner has not shown that either reference or the art provides a motivation to combine the specific elements of Charboneau with Shen to derive the claimed invention (Appeal Br. 9).

We do not find this argument to be persuasive. “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Int’l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007). “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the relevant question is “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 1740. Charboneau discloses reverse phase protein arrays for analyzing, among other things, changes in protein status resulting from treatment of cells with an agent and Shen discloses monitoring the post-translational modification

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of proteins using modification-specific agents, including the use of test arrays and control arrays. The combination of Charboneau's reverse phase protein microarrays with Shen's protein analytical tools and methods appears to be nothing more than the combination of old elements to yield predictable results.

SUMMARY

The Examiner's rejections are supported by the preponderance of the evidence of record. We therefore affirm the rejection of claims 1-4, 8 and 12 under 35 U.S.C. § 103.

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

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