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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/925,382	10/26/2007	Daniel van der Lelie	BSA 08-01	2885

26302 7590 02/21/2013
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EXAMINER
BOESEN, CHRISTIAN C

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
02/21/2013	ELECTRONIC

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DANIEL VEN DER LELIE

Appeal 2011-013187
Application 11/925,382
Technology Center 1600

Before TONI R. SCHEINER, STEPHEN WALSH, and
ULRIKE W. JENKS, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) from the rejection of claims directed to a single point genome signature tag method for analyzing the variety of organisms in a sample. The Patent Examiner rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

"The present invention relates to a method for analyzing the nucleic acid prepared from a specimen to establish the organismic complexity of the sample." (Spec. 4, ¶ [0011].) More particularly, the method is said to involve "analyzing organismic complexity through the identification and analysis of single point genome signature tags (SP-GSTs)." (*Id.* at 6, ¶ [0012].)

Claims 50-55 and 95-98 are on appeal. Claim 50 is representative and reads as follows:

50. A method for analyzing the variety of members of specific phyla or families of organisms contained in a sample using single point genome signature tags comprising the steps of:

a) providing a sample containing one or more organisms;

b) isolating the DNA from the organisms in the sample;

c) contacting the DNA with a fragmenting enzyme under conditions appropriate for substantially complete digestion of the DNA thereby generating a plurality of DNA fragments, each having complementary cohesive termini, said fragmenting enzyme being a type II restriction endonuclease which does not cleave within conserved segments of a gene of focus, said gene of focus being a gene containing segments that are highly conserved across a phylum or a family of organisms and segments that are species-specific across the phylum or family of organisms;

d) incubating the DNA fragments of step c) with a molar excess of a duplex linker having a type IIS restriction enzyme recognition sequences and one cohesive terminus compatible with termini generated by the fragmenting enzyme of step c), under conditions appropriate for ligating one duplex linker to each cohesive terminus of the DNA fragments thereby generating a plurality of DNA fragment-duplex linker species;

e) amplifying a portion of a specific subset of DNA fragment-duplex linker species using a pair of primers comprising a first primer specific for the duplex linker and an anchoring primer, said anchoring primer being specific for a conserved segment of the gene of focus and which anchoring primer is covalently modified with a first member of a

specific binding pair, thereby generating a mixture of unamplified DNA fragment-duplex linker species and amplified portions of a subset of the DNA fragment-duplex linker species, said amplified portions comprising sequences that are conserved across the phylum or family and sequences that are species-specific and which species-specific sequences contain the single point genome signature tags;

f) capturing the amplified portions of the subset by contacting the mixture of step e) with a solid support having an attached second member of the specific binding pair;

g) incubating the solid support and captured amplified portions of step f) with the type IIS restriction enzyme, under conditions appropriate for substantially complete digestion thereby releasing the duplex linkers, each having an appended single point genome signature tag (SP-GST);

h) recovering the released duplex linkers and appended SP-GSTs;

i) incubating the recovered linkers and SP-GSTs of step h) with a molar excess of an amplification adapter, the amplification adapter having one terminus compatible with the termini of the appended SP-GSTs, the incubation being carried out under conditions appropriate for ligating one amplification adapter to each appended SP-GST;

j) recovering the ligation product of step i);

k) determining the nucleotide sequence of a statistically significant number of appended SPGSTs to generate a listing of SP-GSTs; and,

l) relating the listing of SP-GSTs of step k) to DNA sequences in databases to determine analyze the variety of members of specific phyla or families of organisms contained in the sample.

The Examiner rejected all the claims under 35 U.S.C. § 103(a) as unpatentable over Ryo,[1] Zhou,[2] Spinella,[3] Velculescu,[4] Tucholski,[5] and Ahmadian.[6]

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[1] Akihide Ryo et al., *A Modified Serial Analysis of Gene Expression That Generates Longer Sequence Tags by Nonpalindromic Cohesive Linker Ligation*, 277 ANAL. BIOCHEM. 160-162 (2000).

[2] J. Zhou et al., *Molecular characterization and diversity of thermophilic iron-reducing enrichment cultures from deep subsurface environments*, 90 J. APPLIED MICROBIOL. 96-105 (2001).

OBVIOUSNESS

The Issues

The Examiner concluded that it would have been obvious to apply Ryo's analytical method, with some modifications, to Zhou's objective of identifying microbial strains in a sample containing multiple taxonomic units.

Appellant disputes the Examiner's conclusion, arguing that (i) Zhou "did not make such substitution and then utilize the methods of Ryo, Spinella, Velculescu, Tucholski and Ahmadian;" (ii) Zhou "could not use the earlier teachings of Ryo, Spinella, Velculescu, Tucholski and Ahmadian;" and (iii) "the teachings of Ryo and the others could not be applied by Zhou et al., to accomplish the analysis the variety of members of specific phyla or families in the mixed sample." (App. Br. 6.)

Findings of Fact

1. We adopt the Examiner's findings concerning the scope and content of the prior art, and repeat the following findings for discussion purposes.
2. Ryo stated:

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[3] Dominic G. Spinella et al., *Tandem arrayed ligation of expressed sequence tags (TALEST): a new method for generating global gene expression profiles*, 27 NUC. ACIDS. RES. ***e22*** i-viii (1999).
[4] Victor E. Velculescu et al., *Serial Analysis of Gene Expression*, 270 SCIENCE 484-487 (1995).
[5] Janusz Tucholski et al., *MmeI, a class-IIS restriction endonuclease: purification and characterization*, 157 GENE 87-92 (1995).
[6] Afshin Ahmadian et al., *Single-Nucleotide Polymorphism Analysis by Pyrosequencing*, 280 ANAL. BIOCHEM. 103-110 (2000).

> The serial analysis of gene expression (SAGE) method is a highly efficient method for systematically analyzing the pattern of gene expression in tissues or cells, SAGE has been shown to provide a means for the quantitative cataloging of expressed genes in various physiological, developmental, and pathological states. However, because of the difficulty of preparing SAGE, libraries and several drawbacks, especially the very short sequence tags generated, fewer groups have successfully applied this method to biological analyses than another related technique, DNA microarray . . . , regardless of its potential advantages. To circumvent this, we attempted modifications of the SAGE procedure.

(Ryo 160, footnotes and citations omitted.)

3. Ryo stated: "In principle, SAGE should be a powerful tool and it will be applied to a variety of biological studies. The present drastic modifications should provide SAGE analysis with feasibility and reproducible outcomes." (Ryo 162.)

4. Zhou stated: "There is mounting evidence of very high microbial diversity in environmental samples that may offer a largely untapped store of organisms of potential use in biotechnology." (Zhou 96.)

5. Zhou stated:

> the molecular analysis of the differentially grown thermophilic Fe(III)-reducing bacterial cultures provided important information on microbial community structure. The sequence information will facilitate the design of appropriate molecular probes in future analysis of dynamic changes in the Fe(III)-reducing community that can lead to a more precise identification of various Fe(III)reducing bacteria in different environments.
>
> If high diversity is a common feature of enrichment cultures, this phenomenon should be considered in the isolation of bacteria for biotechnology applications. Divergence of 1-5% in l6S rDNA sequence is relatively small from a microbial phylogenetic viewpoint, but these small differences may indicate larger differences in other important physiological aspects. Differences in kinetics, substrates

> used and products produced could be critical in determining the utility of a strain for biotechnology applications. Thus, it might be wise to attempt to obtain and screen more isolates, even if they are 'closely' related, in order to obtain strains with different physiological properties.
>
> (Zhou 104.)

Principles of Law

Patentability is not imparted where "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

Analysis

The rejection is organized in two parts. In the first part, the Examiner makes the findings required by steps one and two of the *Graham* analysis, i.e., (1) determining the scope and content of the prior art, and (2) identifying the differences between Appellant's invention and the prior art. The findings are presented as a step-by-step comparison of claim 50's 12-step method to prior art methods of genetic analysis. (Ans. 7-18.) In the second part, the rejection presents reasons why (i) it would have been obvious to apply Ryo's modified method for serial analysis of genetic expression (SAGE) to Zhou's subject - the analysis of variety of phyla or family members in a sample of organisms, and (ii) other modifications to Ryo's method would have been obvious, such as the particular endonuclease used in step c). (*Id.* at 18-31.)

The genetic material that Ryo, Velculescu, and Spinella each analyzed was from a single species; none of them described analyzing the variety of organisms in a sample, which was taught by Zhou. More specifically, Ryo used its method "to demonstrate an example of gene expression profiles in human hepatocellular carcinoma (HCC) and adjacent noncancerous liver tissue (NCL)." (Ans. 7; Ryo 161.) In Velculescu's paper describing SAGE, "[a]s a demonstration of this approach, SAGE was used to characterize gene expression in the human pancreas." (Velculescu 485.) Spinella demonstrated its process on human lung tissue. (Spinella ii.) Ryo, Velculescu, and Spinella did not apply their methods to analyzing the variety of members of a phyla or family of organisms in a sample, but claim 50's steps e) through h) involve molecules from plural[7] species. (Ans. 11-12.)

Zhou taught analyzing the variety of members of specific families of organisms contained in a sample and isolating "the total community DNA." (Ans. 12.) Zhou described the significance of analyzing the variety of genetic material in samples containing plural organisms. (*E.g.*, FF 4 and 5.) For example, Zhou stated that the genetic analysis of cultures provided "important information" on microbial community structure. (FF 4.) According to Zhou, the obtained sequence information would "facilitate the design of appropriate molecular probes in future analysis of dynamic changes in the Fe(III)-reducing community," which would "lead to a more

[7] Although claim 50 at step a) includes analyzing a sample "containing <u>one</u> or more organisms," thus indicating that the method may cover analyzing a sample with only one organism, step b) recites isolating DNA from "organisms."

precise identification of various Fe(III)reducing bacteria in different environments." (FF 5.)

Given the significance of Zhou's objective, the Examiner concluded it would have been obvious "to provide Ryo's methods of a modified serial analysis of gene expression that generates longer sequence tags by nonpalindromic cohesive linker ligation in Zhou's methods for analyzing the variety of members of specific phyla or families of organisms contained in a sample." (Ans. 18.) Ryo indicated that "SAGE should be a powerful tool and it will be **applied to a variety of biological studies**." (Ans. 19; *see* FF 3.) Zhou indicated that environmental samples "offer **a largely untapped store of organisms of potential use in biotechnology** . . . . it might be wise to attempt to obtain and screen more isolates … in order to obtain strains with different physiological properties." (Ans. 19-20; *see* FF 5.) We agree with the Examiner that Zhou's suggestion of further analysis, and Ryo's indication that its method could be used for a variety of studies, would have suggested applying Ryo's powerful method to Zhou's objective.

The Examiner further noted that Ryo's method was successfully demonstrated on closely related cells. (Ans. 20.) Zhou suggested screening even "closely related" samples (FF 5), and we agree with the Examiner that this evidence supports a reasonable expectation of success in applying Ryo's method to Zhou's samples. The same evidence supports the Examiner's finding that substitution of Zhou's community DNA for the samples Ryo analyzed "would have yielded predictable results," including the successful analysis of Zhou's samples. (Ans. 19.)

Appellant disputes the Examiner's conclusions but does not take issue with the factual findings concerning the scope and content of the prior art,

and the differences between the invention and the prior art. Importantly, Appellant contends that Zhou is the closest prior art "because the analysis produces a listing of 'operational taxonomic units' (OTUs) and in some cases identification of specific families, phyla and species of iron-reducing organisms after analyzing a sample containing a mixture of organisms." (App. Br. 5.) Appellant focuses on the rejection's proposal to substitute Zhou's sample of organisms for Ryo's separate samples of normal versus cancerous liver cells. (*Id.*)

Appellant does not agree that such a substitution would have been obvious, and further argues that (i) Zhou "did not make such substitution and then utilize the methods of Ryo, Spinella, Velculescu, Tucholski and Ahmadian;" (ii) Zhou "could not use the earlier teachings of Ryo, Spinella, Velculescu, Tucholski and Ahmadian;" and (iii) "the teachings of Ryo and the others could not be applied by Zhou et al., to accomplish the analysis the variety of members of specific phyla or families in the mixed sample." (*Id.* at 6.) Appellant contends that if Appellant's invention had been obvious, Zhou would have used it, but did not:

> if the presently claimed invention was obvious to those of skill in the art, Zhou, et al. should have been able to make use of the substitution and then the combined teachings of Ryo, Spinella, Velculescu, Tucholski and Ahmadian so as to then analyze only a small portion of the 16S rDNA sequences of the organisms rather than amplifying and doing RFLP analysis on the entire 16S rDNA region. Instead, they did not.

(*Id.*)

These arguments are unpersuasive. First, the relevant time for assessing obviousness is the effective filing date of Appellant's application (either 2004 or 2002), not the date of Zhou's publication in 2001. Second,

Zhou apparently submitted its paper to the journal April 3, 2000. (*See* Zhou 96, editor's notes.) As Ryo's work was published in 2000, Appellant may be correct that Zhou "could not use" Ryo's method, but the reason is the unavailability of the Ryo information while Zhou was doing its work, not because Zhou could not have applied Ryo's method if it had been available. As all the applied references were available by 2002, Appellant's earliest possible effective filing date, we assess obviousness according to what was known in 2002.

Appellant similarly contends that "**if** the presently claimed invention was indeed obvious through the combination of Ryo, Spinella, Velculescu, Tucholski and Ahmadian, Zhou et al. or others could and would have made the combination long before the present inventors did so." (App. Br. 6.) This argument is also unpersuasive. First, this is not the kind of undisputed fact appropriate for taking notice. *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006). Second, precedent requires that the applicant submit actual evidence of long-felt need as opposed to argument. This is because "[a]bsent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Id.* at 990-91 (quotations and citations omitted). *See also*, *In re McGuire*, 416 F.2d 1322, 1327-28 (CCPA 1969) ("Appellants argue the century-old status of the references but this argument does not impress us, absent some showing that the art tried and failed to solve some problem notwithstanding its presumed knowledge of the references. For aught that appears, as soon as the need for an inside tubing cutter was perceived it was produced out of the accumulated skill of the art.").

Appellant contends that "[f]ormulation of an obviousness rejection based upon the predictability of substitution of one known element for another in the inherently unpredictable biological sciences is arguably questionable." (App. Br. 7.) Obviousness requires only a reasonable expectation of success; "arguably questionable" is not the standard. The Examiner directed attention to Ryo's statement that SAGE was a "**highly efficient method for systematically analyzing the pattern of gene expression in tissues or cells**." (*See* Ans. 22; FF 2.) Ryo supports the finding and further explains that "SAGE has been shown to provide a means for the quantitative cataloging of expressed genes in various physiological, developmental, and pathological states." (FF 2.) The Examiner found, and Appellant does not dispute, that Ryo's powerful method worked for closely related DNAs. (Ans. 19.) Appellant provides no evidence that a person of ordinary skill in the art would have doubted the likely success of applying Ryo's modified method to Zhou's screening. We conclude that the Examiner's evidence is sufficient to shift the burden to Appellant to do more that say success was "arguably questionable."

Appellant notes other substitutions to Ryo's method the Examiner concluded would have been obvious, but does not show that the Examiner erred in the findings or conclusions. (App. Br. 8-9.) We have reviewed the evidence concerning each of these features. We find the evidence supports the Examiner's findings and that the Examiner reasonably explained the conclusion of obviousness for each proposed change to Ryo's method.

Claims 51-55 and 95-98 have not been argued separately and therefore fall with claim 50. 37 C.F.R. § 41.37(c)(1)(vii).

SUMMARY

We affirm the rejection of claims 50-55 and 95-98 under 35 U.S.C. § 103(a) as unpatentable over Ryo, Zhou, Spinella, Velculescu, Tucholski, and Ahmadian.

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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