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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte SUSAN KIRCHER, JON E. SALOMON, and SHERYL DOUGLAS-MCKAY

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Appeal 2018-002838
Application 11/958,827[1]
Technology Center 1600

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Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a medium for detecting and differentiating species of enterococci, which have been rejected as indefinite and/or obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm the indefiniteness rejection and reverse the obviousness rejection.

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[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 Becton, Dickinson & Co. (Appeal Br. 1.)

STATEMENT OF THE CASE

Enterococci are bacteria that "are normal inhabitants of the gastrointestinal (GI) tract of humans and most animal." (Spec. ¶ 3.) However, "[c]olonization with these organisms often precedes infection, including infection of the urinary tract, intra-abdominal cavity, and the lining of the heart (*i.e.*, endocarditis)." (*Id.*) Unfortunately, strains of Enterococci that have been associated with increased mortality are resistant to vancomycin,[2] which is the current antibiotic treatment of choice for multi-drug resistant organisms. (*Id.* ¶ 4.) Appellant's invention is directed to a medium for use in the detection of vancomycin-resistant *enterococci*. (*Id.* ¶ 2.)

Claims 8, 11, 12, 23, 25–36, 38, and 51 are on appeal. Claim 25 is representative and reads as follows:

> 25. A medium for detecting and differentiating species of enterococci comprising:
>
> a first substrate conjugated to a first imaging moiety, wherein the first substrate preferentially interacts with a first enzyme that is produced by a first species of enterococci compared to a second enzyme that is produced by a second species of enterococci; and
>
> a second substrate conjugated to a second imaging moiety, wherein the second substrate preferentially interacts with the second enzyme that is produced by the second species of enterococci compared to the first enzyme that is produced by the first species of enterococci;
>
> an inhibitor of non-vancomycin resistant enterococci comprising vancomycin;

[2] Such vancomycin resistant *enterococcus* species are referred to in the prior art as VRE. (*See, e.g.*, Hanson Abs.)

a third substrate;

and cefoxitin;

wherein the third substrate, but not the first and second substrates, induces the production of the first enzyme by at least a third species of enterococci that produces the second enzyme without inducement;

wherein the first imaging moiety images a first indicator when the first substrate interacts with the first enzyme and the second imaging moiety images a second indicator when the second substrate interacts with the second enzyme;

and the combined presence of the first imaging moiety and second imaging moiety image a third indicator in the combined presence of the first enzyme and the second enzyme produced by the third species of enterococci,

wherein, the first second and third indicators are perceptually different from each other;

and wherein the cefoxitin in combination with vancomycin either inhibits the growth of the third species of enterococci but not the growth of the first or second species of enterococci or the third species of enterococci overcomes the inhibition wherein the third indicator indicates that the third species overcame the inhibition.

(Appeal Br. 20–21.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Chen	WO 98/04674	Feb. 5, 1998
Chen	US2002/0132285 A1	Sept. 19, 2002
Chen	US6355449 B1	Mar. 12, 2002
Orenga	US 2008/0145879 A1	June 19, 2008
Badal	WO 92/12257	July 23, 1992
Hanson et al., *Comparison of Simple and Rapid Methods for Identifying Enterococci Intrinsically Resistant to Vancomycin*, 37(3) J. Clin. Microbiol., 815–17 (1999)		
S. Vincent et al., *Vancomycin resistance in Enterococcus gamnarum*, 36(7) Antimicrob. Agents Chemother., 1392–99 (1992)		

The following grounds of rejection by the Examiner are before us on review:

Claims 8, 11, 12, 23, 25–36, 38, and 51 under 35 U.S.C. § 103(a) as unpatentable over Chen (any one of '674, '285 and '449), Orenga, Badal, Hanson, and Vincent.

Claim 38 under 35 U.S.C. § 112, second paragraph as being indefinite for being dependent from cancelled claim 37.[3]

DISCUSSION

The Examiner finds that each of the Chen references teach a medium for detecting *E. faecalis*, *E. faecium*, *E. casseliflavus*, and *E. gallinarum*, which are vancomycin resistant *Enterococci*, that comprises a first and

[3] In its Reply Brief, Appellant concedes that claim 38 on appeal does depend from claim 37 (Reply Br. 1–2), a concession with which we agree, as reflected in the Amended Appeal Brief Claims Appendix filed August 30, 2017. Because Appellant does not contest the section 112 rejection as applied to claim 38, that rejection is summarily affirmed.

second substrate of which is conjugate to an image moiety and where the substrates "are selected to interact with a first and second enzyme produced by different species of microorganism." (Final Action 4.) The Examiner further finds that the medium also includes vancomycin and cephalosporins, such as cefoxamine, as well as other inhibitors. (*Id.*)

The Examiner finds Orenga teaches a medium for distinguishing species of a microorganism that includes two substrates selected to interact with different enzymes produced by different microorganism species and which are conjugated to chromophores. (*Id.*) The Examiner also finds that, like Chen, Orenga teaches including vancomycin and cephalosporins and other inhibitors in the medium. (*Id.* at 5.) Orenga specifically indicates the use of vancomycin and cephalosporins for distinguishing *Enterococci*. (*Id.*) The Examiner further finds that Orenga teaches using "the substrates alpha-D-glucopyranoside, beta-D-galactopyranosidase and methyl-alpha-D-glucopyranosidase (0370-0378, Ex. 4) to identify *E. faecalis, E. faecium* and *E. casseliflavus* and *E. gallinarum*." (*Id.*) The Examiner further finds that Orenga teaches the use of a combination of antimicrobials to distinguish between three different species of microorganisms, as well as using a third substrate. (*Id.*)

The Examiner finds that Vincent teaches that it was known that *E. gallinarum* expresses low-level resistance to glycopeptide antibiotics, e.g., vancomycin, and that this resistance is overcome with cephalosporins. (Final Action 6.) The Examiner also finds that Vincent teaches "there is a synergistic effect of the combination on vancomycin resistance in *E. gallinarum* (a VanC phenotype) which differs from both *E. faecalis, E. faecium* (vanA and VanB phenotypes)." (*Id.*)

The Examiner further finds that Hanson teaches that (1) *E. faecalis* and *E. faecium* have a high-level vancomycin resistance while *E. gallinarum* and *E. casseliflavus* express low-level resistance and, in fact, "will grow in/on vancomycin containing media" and (2) the substrate methyl-α-D-glucopyranoside (MGP) can be used to determine whether *E. gallinarum* and *E. casseliflavus* are present in a sample as compared to *E. faecalis* and *E. faecium* because *E. faecalis* and *E. faecium* are negative in an MGP analysis whereas *E. gallinarum* and *E. casseliflavus* are positive. (Final Action 6.)

In light of the foregoing teachings, the Examiner determines that the prior art "clearly teach a first, second and third claimed substrate for distinction among Enterococci species" (*id.* at 5) and that Vincent would have motivated the use of vancomycin and a cephalosporin for use in determining the presence of *E. gallinarum* and Hanson would have motivated one having ordinary skill in the art to include MGP as a third substrate to detect a third Enterococci species since the MGP substrate can differentiate vanC Enterococci species, which include *E. gallinarum*, from *E. faecalis* and *E. faecium* (*id.* at 6–7).

We agree with the Examiner that the combination of references suggests a medium for differentiating three different species of *Enterococcus* that includes vancomycin and cephalosporin and three substrates that are species specific. But we do not agree that the Examiner has established the claimed medium is prima facie obvious.

Orenga teaches different medium for detecting at least three different microorganisms in a sample (Orenga ¶ 109) where the different microorganisms can be different species within the same genus (Orenga ¶ 257 ("This third embodiment of the invention makes is possible to

distinguish, in the same sample, a first and a second group comprising the same species of microorganisms"), ¶ 282 (the "third embodiment of the invention is not limited to distinguishing 3 groups of microorganisms, but may make it possible to distinguish 4, 5 or even more groups of microorganisms.").) Orenga teaches that markers for differentiating microorganism groups means the use of a "specific substrate" "which does not have the same properties on a first and on a second group." (Orenga ¶¶ 40–41.) While not exemplified, Orenga suggests use of three different substrates for detecting three different species particularly because it describes using as many substrates in the context of identifying three different genera of microorganisms. (*Id.* ¶¶ 283–293).

In other words, one of ordinary skill in the art would have reasonably understood from Orenga's teaching that three different substrates could be used in a medium for distinguishing species of microorganisms just as it could be used to distinguish between genera of microorganism. *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) ("In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.") (Internal quotations omitted.) Thus, we disagree with Appellant that Orenga "does not disclose or suggest a medium that is even capable of delivering a perceptual differen[ce] among three VRE species." (Appeal Br. 11.) While Orenga exemplifies only the use of 2 different substrates conjugated to a chromogen for differentiating

Enterococcus species that are species specific (Orenga Example 4), it nevertheless suggests the use of a third substrate.[4]

Additionally, contrary to Appellant's argument (e.g., Reply Br. 8), we agree with the Examiner that the references together suggest a medium that includes vancomycin and a cephalosporin when detecting vancomycin-resistant *Enterococci* species. Chen teaches including both vancomycin and a cephalosporin (cefotaxime) in the same medium when using the medium for assessing the presence of *Enterococci* species. (*See* Chen '674[5] at 35/2 Component II, and 17–18.) We also agree with the Examiner that Orenga teaches a medium that includes vancomycin and an additional inhibitor, such as cefotaxime. (Orenga ¶¶ 49, 57, 211–14, 220–226.)

Vincent teaches that *E. gallinarum* is weakly vancomycin resistant and that the resistance can be overcome with a cephalosporin, such as cefoxitin and cefotaxime. (Vincent 1394 (Table 3), 1397.) Vincent also teaches that vanA and vanB resistant *Enterococci* have a different

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[4] We also agree with the Examiner that Chen, similar to Orenga, is concerned with two or more nutrient indicators that yield distinctively different detectable signals so as to distinguish between species of microorganisms. (*See, e.g.*, Chen '674 at 6.) That Chen may use "sequential detection" of the nutrient indicators so that there is no detectable signal interference (Appeal Br. 9) is not relevant to whether or not the medium claimed, which requires, *inter alia*, the presence of two different substrates, is obvious over the cited prior art. That is because Chen's method of detection of the imaging moiety conjugated to the substrate is not necessary to address whether the claimed first and second substrates of the medium are present and are conjugated to an imaging moiety and that the moiety "images" an indicator after the substrate interacts with an enzyme produced from a species of *Enterococci.*

[5] We only refer to Chen '674, but understand the disclosures of each of the Chen references cited by the Examiner to be substantially similar.

phenotype, e.g., their vancomycin resistance is not overcome with cephalosporins. (Vincent 1397.) Vincent further teaches that *E. faecium* is a vanB bacteria and that *E. faecalis* is a vanA bacteria. (*See id.* at 1393 (Table 1.) Hanson teaches the importance of identifying VRE (Hanson 815). Thus, one of ordinary skill in the art would have found it obvious to include a substrate that would detect whether the weakly resistant *E. gallinarum* was present in a sample should the resistance not be overcome with the cephalosporin suggested for use in the medium by both Chen and Orenga. Hanson teaches such a substrate is MGP because *E. gallinarum* (and *E. casseliflavus*) can acidify MGP but *E. faecalis* and *E. faecium* cannot. (Hanson 815 (a change in the color from red to yellow is indicative of a positive result), 816 (Table 1).)

Nevertheless, despite the foregoing analysis, we do not agree with the Examiner that the references relied upon render obvious a composition where the first and second substrate are conjugated to first and second imaging moieties, respectively, that *in combination* image a third indicator indicative of the third species of *Enterococcus*. That is because we find Orenga teaches that in assessing three or more different species of the same group of microorganisms, one of those species is growth inhibited by the antimicrobial and the remaining species are distinguished by markers that are in the medium that are specific to each of the different species that will grow in the medium. (*See, e.g.*, Orenga ¶¶ 94–98, 257, 282, 368, 382, 384.) Furthermore, Chen teaches independent detection of the different nutrient indicators to determine the presence of a particular bacteria. (Chen '674 at 6.) Chen indicates that the approach it takes by using a second nutrient indicator that produces a colorless intermediate first before reacting it with a

developing agent "prevents interference from the colored product of the first nutrient indicator" in detecting a second bacteria. (*Id.* at 6–7.) Thus, we agree with Appellant (although for a somewhat different reason) that Chen teaches away from employing a mixture of chromogenic indicators to detect one particular species.

We agree with the Examiner that by including MGP, as the third substrate, which is reasonably suggested by Hanson as a specifies specific substrate for *E. gallinarum* and not for *E. faecalis* and *E. faecium* (Hanson 816 Table 1), the repressed enzyme in *E. gallinarum* that is the same enzyme that is produced by a first species of *Enterococci*, would inherently be activated, provided that *E. gallinarum* broke through the vancomycin-cephalosporin inhibition. (Ans. 10.) But that is not the same thing as finding that the combined presence of the first imaging moiety and second imaging moiety "image a third indicator in the combined presence of the first enzyme and the second enzyme produced by the third species of enterococci," i.e., the combined presence of the first and second imaging moiety indicate the third species of *enterococci* where Orenga suggests the inclusion of a different colored marker specific to a species for all non-growth inhibited microorganisms.

Orenga does not recognize the ability of a medium without a third chromogenic imaging moiety to image a third species and Chen teaches there can be a problem of interference from colored products masking one another (Chen '674 at 6.). "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 9 F.3d

1531, 1534 (Fed. Cir. 1993) (internal citations and quotations omitted); *see also PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (distinguishing a prior case finding obviousness based on inherency because, in that case, "neither party disputed that the [claimed features] were *expected* in light of the dosages disclosed in the prior art" (emphasis added)) Nor is there any evidence that Orenga actually generated a medium that would anticipate the instant claims.

We conclude that it is only by hindsight that one would arrive at a medium required by claim 25

> wherein the first imaging moiety images a first indicator when the first substrate interacts with the first enzyme and the second imaging moiety images a second indicator when the second substrate interacts with the second enzyme;
>
> and the combined presence of the first imaging moiety and second imaging moiety image a third indicator in the combined presence of the first enzyme and the second enzyme produced by the third species of enterococci.

Consequently, we reverse the Examiner's rejection of claims 8, 11, 12, 23, 25–36, 38, and 51 under 35 U.S.C. § 103(a) as unpatentable over Chen (any one of '674, '285 and '449), Orenga, Badal, Hanson, and Vincent.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
38	112, second paragraph		38	
8, 11, 12, 23, 25–36, 38, 51	103(a)	Chen '674, Chen '285, Chen '449,		8, 11, 12, 23, 25–36, 38, 51

		Orenga, Badal, Hanson, Vincent		
Overall Outcome			38	8, 11, 12, 23, 25–36, 51

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART