

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

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*Ex parte* ALLAN BRADLEY and WEI-WEN CAI

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Appeal 2008-1184  
Application 10/207,440  
Technology Center 1600

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Decided: May 19, 2008

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Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and  
FRANCISCO C. PRATS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

**DECISION ON APPEAL**

This is an appeal under 35 U.S.C. § 134 involving claims to a method for hybridizing fluorescently labeled target nucleic acids to nucleic acid probes. The Examiner has rejected the claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.<sup>1</sup>

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<sup>1</sup> In this decision we consider only those arguments actually made by Appellant. Arguments that Appellant could have made but chose not to

STATEMENT OF THE CASE

Claims 28-34 are on appeal (App. Br. 2).<sup>2</sup> Claims 29-35 have been withdrawn from consideration by the Examiner (*id.*). Claim 28 is representative of the appealed subject matter and reads as follows:

28. A method for hybridizing a sample of labeled nucleic acid targets to a plurality of nucleic acid probes, comprising: providing a sample of nucleic acid targets comprising fluorescent-labeled nucleic acid fragments and a plurality of nucleic acid probes, wherein the fluorescent label is sensitive to oxidation; and contacting the nucleic acid target and nucleic acid probe under conditions allowing hybridization of the sample with the probe, wherein the hybridization conditions comprise use of a hybridization solution comprising at least one antioxidant, wherein the antioxidant is present in the hybridization solution at a concentration of about 25 mM to about 1000 mM, and wherein the amount of antioxidant in the solution is sufficient to inhibit oxidation of the fluorescent label under the hybridization conditions.

The Examiner applies the following documents in rejecting the claims:

Rothberg<sup>3</sup>                      US 6,335,423 B1                      Mar. 12, 2002

C. C. Winterbourn et al., *Reactivity of Biologically Important Thiol Compounds with Superoxide and Hydrogen Peroxide*, 27 *Free Radical Biology & Medicine* 322-328 (1999)

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make in the Briefs have not been considered and are deemed to be waived. See 37 C.F.R. § 41.37(c)(1)(vii).

<sup>2</sup> Appeal Brief filed January 4, 2007.

<sup>3</sup> While the Examiner relies on the Rothberg and Winterbourn references to show that claims are unpatentable, the references are not cited in the “Evidence Relied Upon” section of the Examiner’s Answer (*see* Ans. 2-3 (mailed June 21, 2007)).

R. S. Davidson et al., *The Effects of Enzymes on the Photobleaching of Fluorescein and Fluorescein Isothiocyanate Conjugates*, 1 Journal of Photochemistry and Photobiology, B: Biology 361-369 (1988).

3 Dictionary of Organic Compounds 2516 (6<sup>th</sup> ed. 1996).

The following rejections are before us for review:

Claims 28-30, 32, and 33 stand rejected under 35 U.S.C. § 102(e) as anticipated by Rothberg, as evidenced by Davidson and the Dictionary of Organic Compounds (Ans. 4-6).<sup>4</sup>

Claim 31 stands rejected under 35 U.S.C. § 103(a) as being obvious in view of Rothberg as evidenced by Davidson (Ans. 6-7).

Claim 34 stands rejected under 35 U.S.C. § 103(a) as being obvious in view of Rothberg, as evidenced by Davidson, the Dictionary of Organic Compounds, and Winterbourn (Ans. 7-8).

#### ANTICIPATION

##### *ISSUE*

The Examiner cites Rothberg as teaching “a method for hybridizing a sample of labeled nucleic acid targets to a plurality of nucleic acid probes” (Ans. 4). The Examiner states that, because Davidson discloses that fluorescent labels such as fluorescein are susceptible to oxidation in aqueous solutions, Rothberg’s fluorescently labeled target molecules are inherently sensitive to oxidation (*id.* at 4-5).

The Examiner states that Rothberg discloses “contacting the nucleic acid targets with the probes by hybridizing the targets to the probes on [an] array” in a hybridization solution that “contains 10 mM DTT (col. 61, lines

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<sup>4</sup> Examiner’s Answer mailed June 21, 2007.

30-35), which, according to Applicants' example and definition, is an antioxidant" (*id.* at 5). The Examiner cites the Dictionary of Organic Compounds solely to show that Rothberg's DTT is a mercapto-containing compound (*id.* at 6), a fact Appellants do not dispute.

The Examiner contends that the 10 mM DTT used in Rothberg's hybridization solution inherently meets the limitation of claim 28 requiring the antioxidant to be present in amount sufficient to inhibit oxidation of the fluorescent label because Appellants' Specification discloses that 10 to 500 mM DTT was sufficient to inhibit the oxidation of fluorescent label (*id.* (citing Spec. 30)). The Examiner further contends that because the term "about" is not defined in the Specification, "any antioxidant concentration is interpreted as being 'about 25 mM' or 'about 50 mM'" (Ans. 3). Therefore, the Examiner finds, the 10 mM DTT used by Rothberg is "within the range of about 25 mM to about 1000 mM and from about 50 mM to about 500 mM" (*id.* at 5).

Appellants contend that "Rothberg does not anticipate any of claims 28-30, 32 or 33" (App. Br. 4). Specifically, Appellants contend that it was improper for the Examiner to rely on Appellants' disclosure to determine whether Rothberg's hybridization solution inherently met the limitation requiring the antioxidant to be present in an amount sufficient to inhibit oxidation of the fluorescent label (*id.* at 4-5). Appellants contend that "[n]o evidence has been provided that Rothberg necessarily discloses the claimed antioxidant concentration" (*id.* at 5). Appellants further contend that because the meaning of the term "about" is clear in view of the Specification, "it is improper to interpret the claimed element 'about 25 mM to about 1000 mM' to mean any concentration of antioxidant" (*id.* at 6).

Appellants place all of the claims subject to this ground of rejection together in a single group, “with claim 28 being representative” (*id.* at 4). The issue with respect to this rejection, therefore, is whether the Examiner erred in finding that Rothberg meets all of the limitations recited in claim 28.

*FINDINGS OF FACT*

1. Claim 28 recites a process having the following steps:

(a) providing a sample of nucleic acid targets comprising fluorescent-labeled nucleic acid fragments and a plurality of nucleic acid probes, wherein the fluorescent label is sensitive to oxidation; and

(b) contacting the nucleic acid target and nucleic acid probe under conditions allowing hybridization of the sample with the probe.

Claim 28 requires the solution used in the hybridization step to contain at least one antioxidant at a concentration of “about 25 mM to about 1000 mM.” Claim 28 also requires the amount of antioxidant in the solution to be “sufficient to inhibit oxidation of the fluorescent label under the hybridization conditions.”

Claims 31 and 32 are also relevant in assessing the merits of the Examiner’s anticipation rejection. Claim 31 recites “[t]he method of claim 28, wherein the antioxidant is present in the hybridization solution at a concentration of 25 mM to 1000 mM.”

Claim 32 recites “[t]he method of claim 31, wherein the antioxidant is present in the hybridization solution at a concentration of about 50 mM to about 500 mM.”

2. The Specification discloses that, in hybridization experiments, “fluorescent signals were significantly stronger when the antioxidant dithiothreitol (DTT) was added to the hybridization buffer as compared to

hybridization reactions lacking an antioxidant. Furthermore, the extent of ‘protection’ against oxidation (i.e., stabilization of the fluorescent dye Cy5<sup>TM</sup>) increased as the concentration of antioxidant increased (from 10 mM to 500 mM)” (Spec. 30).

3. The Specification states:

Hybridization and wash solutions used in CGH [(comparative genomic hybridization)] and arrays are known in the art, see, e.g., Cheung (1999) Nature Genetics Supp. 21:15-19; see also, definitions discussion, above. The concentration of antioxidant in those solutions depends on a variety of factors: e.g., the composition of the hybridization or wash buffer; the concentration of composition to be “protected” from oxidation (e.g., Cy5<sup>TM</sup>), the hybridization and wash conditions (e.g., length of time, heat, humidity, etc.). Thus, in various embodiments, the amount of antioxidant in a hybridization, wash or other solution, can be, e.g., at a concentration of about 25 mM to about 1 M, about 50 mM to about 750 mM, about 50 mM to about 500 mM, and about 100 mM to about 500 mM. However, any appropriate concentration of antioxidant or free radical scavenger can be used to practice the invention.

(Spec. 24-25).

4. Rothberg discloses methods whereby “[u]niversal device arrays (‘UDAs’), consisting of arrays of probes . . . , are used for the parallel and simultaneous observation of terminal subsequences of target nucleic acids from a complex mixture of target nucleic acids” (Rothberg, col. 57, ll. 48-52). Once target nucleic acids are hybridized to the probe array, “UDAs can be used to generate terminal subsequence recognition signals according to various methods,” including “the hybridization/ligation method (‘h/l’ method)” (*id.* at col. 57, ll. 57-60).

5. Rothberg discloses that the h/l method uses ligase enzymes' specificity for exactly complementary double stranded nucleic acids to discriminate between specifically bound and mismatched duplexes (*see, e.g.*, Rothberg, col. 58, ll. 5-20). Thus, "[p]referably, the ligase is in the [hybridization] solution and ligation occurs simultaneously with hybridization" (*id.* at col. 61, ll. 39-41).

6. Rothberg states that "FIG. 6B illustrates the method steps of the hybridization/ligation method" (Rothberg, col. 61, ll. 22-23). Figure 6B shows the initial hybridization mixture with target nucleic acid 610 labeled with fluorescent label FAM (*see id.* at col. 91, ll. 11-12), array-bound complementary probe 611, and "stacking oligonucleotide 612," which stabilizes the hybridized probe-target complex (*see id.* at col. 58, l. 27 through col. 59, l. 44).

7. Regarding the conditions for hybridization in the h/l method, Rothberg discloses that "[t]ypically, hybridization occurs in a total volume of 10  $\mu$ l (placed over a UDA of 1.8 cm X 1.8 cm size and covered by a cover slip) of a solution containing 1 pM of target nucleic acids, 10% PEG ( $M_w$  6000), 66 mM Tris.Cl, 6.6 mM MgCl<sub>2</sub>, 10 mM DTT, 1 mM ATP and 40 mM NaCl (pH 7.5) at 25° C. for 80 min" (Rothberg, col. 61, ll. 30-35).

8. The abstract of Davidson states that "fluorescein is susceptible to bleaching in the presence of organic peroxides, hydroperoxides and oxyradicals. The effectiveness with which enzymes, which can inhibit oxidation processes, retard the photo- bleaching of fluorescein isothiocyanate conjugates indicates that dye/protein oxidation products are involved in the mechanism of dye fading" (Davidson 361 (abstract)).

*PRINCIPLES OF LAW*

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

It is well settled that, “[t]o anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently.” *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

However, as stated in *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977) (quoting *In re Swinehart*, 439 F.2d 210, 212-13 (CCPA 1971):

[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

It is also well settled that, during examination, the PTO must interpret terms in a claim using “the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant’s specification.” *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

“The use of the word ‘about,’ avoids a strict numerical boundary to the specified parameter.” *Ortho-McNeil Pharmaceutical, Inc. v. Caraco*

*Pharmaceutical Laboratories, Ltd.*, 476 F.3d 1321, 1326 (Fed. Cir. 2007) (quoting *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed.Cir.1995)); *see also In re Harris*, 409 F.3d 1339, 1343 (Fed. Cir. 2005) (“[U]se of the term ‘about’ shows that the applicants did not intend to limit the claimed ranges to their exact end-points.”).

Moreover, “the word ‘about’ does not have a universal meaning in patent claims[;]” rather, “the meaning depends on the technological facts of the particular case.” *Pall Corp.*, 66 F.3d at 1217; *see also Eiselstein v. Frank*, 52 F.3d 1035, 1039 (Fed. Cir. 1995) (“The meaning of the word ‘about’ is dependent on the facts of the case, the nature of the invention, and the knowledge imparted by the totality of the . . . disclosure to those skilled in the art.”). Thus, in evaluating the scope of the “about,” it is appropriate to look at how the Specification and other claims use the term, as well as considering the effects of varying the parameter described by the term. *Pall Corp.*, 66 F.3d at 1217.

#### *ANALYSIS*

We do not agree with Appellants that the Examiner failed make out a prima facie case of anticipation with respect to claim 28.

As required by claim 28, Rothberg discloses a process in which fluorescently labeled target nucleic acid fragments are contacted with nucleic acid probes under hybridizing conditions (*see* FF 6). Appellants do not dispute that the fluorescent label disclosed in Rothberg’s Figure 6B, “FAM,” is sensitive to oxidation; moreover, given Davidson’s disclosure that the fluorescent dye fluorescein is susceptible to oxidation, we agree with the Examiner that it was reasonable to conclude that Rothberg’s fluorescent label is “sensitive to oxidation” as required by claim 28.

We also agree with the Examiner that it was reasonable to conclude that the 10 mM DTT used in Rothberg's hybridization solution (*see* FF 7), meets claim 28's limitation requiring an antioxidant to be present in an amount "sufficient to inhibit oxidation of the fluorescent label under the hybridization conditions." Specifically, Rothberg's DTT is the same antioxidant as that disclosed in the Specification as being useful for inhibiting the oxidation of the fluorescent dye Cy5<sup>TM</sup> (*see* FF 2). Also, the 10 mM concentration of DTT in Rothberg's hybridization solution is within the 10 to 500 mM DTT concentration range disclosed in the Specification as protecting the fluorescent dye (*see* FF 2). Thus, given the reasonableness of the Examiner's finding, the burden shifts to Appellants to show that the claimed process differs from the prior art with respect to this limitation. *See In re Best*, 562 F.2d at 1255.

Appellants argue that "[i]t is well established that use of Appellants' disclosure as a blueprint or roadmap for a rejection is improper and constitutes impermissible hindsight" (App. Br. 4 (citing *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971); *see also* Reply Br. 6). Appellants argue that, because the conditions of Rothberg's hybridization are not identical to those disclosed in the Specification, it is improper to assume that Rothberg's DTT will provide the claimed oxidation-inhibiting effect, absent some objective evidence (App. Br. 5; *see also* Reply Br. 6-7). Moreover, Appellants argue, anticipation cannot be shown by mere probability or possibility (App. Br. 5).

We are not persuaded by these arguments. The holding in *In re McLaughlin* relates to the proper sources of motivation for combining references in an obviousness rejection. *See McLaughlin*, 443 F.2d at 1395.

The rejection immediately at issue is an anticipation rejection. Motivation is irrelevant to an anticipation analysis. *See, e.g., Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998) (“[T]he question whether a reference ‘teaches away’ from the invention is inapplicable to an anticipation analysis.”).

Moreover, it is well settled that it is proper to consult the Specification to determine the scope and meaning of claim terms. *See In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Thus, we agree with the Examiner that it was proper to consult the Specification to determine what concentrations of which antioxidants are “sufficient to inhibit oxidation of the fluorescent label under the hybridization conditions,” as recited in claim 28. Also, because claim 28 does not recite any particular level of oxidation inhibition, claim 28 encompasses even miniscule levels of inhibition.

Therefore, because claim 28 encompasses small amounts of inhibition, and because Rothberg uses the same antioxidant used in the Specification, at a concentration disclosed in the Specification as providing significant oxidation inhibition, we agree with the Examiner that it was reasonable to conclude that Rothberg’s 10 mM DTT in the hybridization buffer was “sufficient to inhibit oxidation of the fluorescent label under the hybridization conditions,” as required by claim 28.

Appellants argue that the scope of the term “about” is clear from the Specification (App. Br. 6; *see also* Reply Br. 8). Specifically, Appellants urge that “about” has a flexible meaning, and that “[t]herefore, it is improper to require Appellants to limit the term ‘about’ to a particular range or interval. In addition, under no circumstances would the term ‘about’ expand a claimed range or value to mean any range or value, as erroneously

proffered” (App. Br. 6). Appellants point in particular to the disclosure in the paragraph spanning pages 24 and 25 of the Specification, noting that “[i]n no instance in Par. No. [0083]<sup>5</sup> . . . does the antioxidant concentration extend below ‘about 25 mM.’ In addition, even if the antioxidant concentration was described in Par. No. [0083] to extend well below ‘about 25 mM,’ it is immaterial because such a concentration is not claimed in claim 28” (App. Br. 6).

We are not persuaded by these arguments. While it might not be reasonable to interpret claim 28 to encompass any antioxidant concentration (Ans. 3), we agree with the Examiner that it was reasonable to interpret claim 28’s recitation, “antioxidant . . . present in the hybridization solution at a concentration of about 25 mM to about 1000 mM,” to encompass Rothberg’s hybridization solution that contains 10 mM DTT.

The Specification does not define the term “about.” The Specification discloses four useful ranges for the antioxidant, “about 25 mM to about 1 M, about 50 mM to about 750 mM, about 50 mM to about 500 mM, and about 100 mM to about 500 mM” (Spec. 25 (FF 3)). In addition to disclosing those concentrations as being useful, the Specification states that “any appropriate concentration of antioxidant or free radical scavenger can be used to practice the invention” (*id.*). Also, claim 32 recites that “the antioxidant is present in the hybridization solution at a concentration of about 50 mM to about 500 mM.”

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<sup>5</sup> The paragraph spanning pages 24 and 25 of the Specification corresponds to paragraph [0083] of Appellants’ published application, U.S. Patent Application Publication No. US 2003/0003496 A1, published on January 2, 2003.

Thus, given the relatively large breadth of useful antioxidant concentrations encompassed by the ranges disclosed in the Specification and claims, the wide variation in endpoints in the disclosed ranges, and the Specification's disclosure that antioxidant concentrations outside those explicitly mentioned can be useful in practicing the invention, we agree with the Examiner that it was reasonable to conclude that the term "about" should be given a relatively expansive, rather than narrow, interpretation. Moreover, since the word "about" is a term of approximation, it is reasonable to interpret "about 25 mM to about 1000 mM" as in claim 28 to include values outside the explicitly recited endpoints. Given an expansive meaning for "about," and the fact that the 10 mM DTT in Rothberg's hybridization solution differs from the "about 25 mM" endpoint in claim 28 by a number much smaller than the total range of useful concentrations recited in claim 28, we also agree with the Examiner that it was reasonable to interpret claim 28 as encompassing the amount of DTT in Rothberg's hybridization solution.

Thus, for the above reasons we agree with the Examiner that Rothberg discloses a process that meets all of the limitations in claim 28. We therefore affirm the Examiner's anticipation rejection of claim 28 over Rothberg. Because they were not argued separately, claims 29, 30, and 33 fall with claim 28. *See* 37 C.F.R. § 41.37(c)(1)(vii).

While Appellants place all of the claims subject to this ground of rejection together in a single group, "with claim 28 being representative" (App. Br. 4), Appellants appear to argue claim 32 separately, urging that "Rothberg does not disclose the antioxidant concentration of claim 32, which recites an antioxidant concentration of about 50 mM to about 500

mM” (App. Br. 5). However, as discussed above, we agree with the Examiner that the term “about” should be given a relatively expansive interpretation in light of the Specification’s use of that term. For reasons similar to those discussed above, we also agree with the Examiner that Rothberg anticipates claim 32.

In summary, we affirm the Examiner’s rejection of claims 28-30, 32, and 33 as anticipated by Rothberg.

#### OBVIOUSNESS -- CLAIM 31

##### *ISSUE*

Claim 31 stands rejected under 35 U.S.C. § 103(a) as being obvious in view of Rothberg as evidenced by Davidson (Ans. 6-7).

The Examiner states that “Rothberg et al. teach a concentration of DTT (= antioxidant) of 10 mM, but do not teach concentration of 25 to 1000 mM” (*id.* at 6). The Examiner nonetheless concludes that the amount of antioxidant recited in claim 31 would have been obvious to a person of ordinary skill in view of Rothberg because “where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation” (*id.* at 6-7 (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955))).

Appellants contend that, because neither Rothberg nor Davidson discloses the concentration of DTT as a result-effective variable, claim 31 is patentable over those references (App. Br. 7). Moreover, Appellants argue, because Rothberg did not use DTT in its hybridization solutions, “Rothberg could not have recognized that the use of DTT inhibited oxidation of a fluorescent label. By extension, because Rothberg did not recognize the use of DTT as an antioxidant in hybridization solutions, it would not have been

obvious for Appellants to perform the optimization of the concentration ranges recited in claim 31” (*id.* at 7-8; *see also* Reply Br. 10). Appellants further contend that a person of ordinary skill would not have been motivated to combine the teachings of the two references (App. Br. 8)

The issue with respect to this rejection, therefore, is whether Appellants have shown that the Examiner erred in concluding that one of ordinary skill would have considered claim 31 obvious in view of Rothberg and Davidson.

#### *FINDINGS OF FACT*

9. Claim 31 recites “[t]he method of claim 28, wherein the antioxidant is present in the hybridization solution at a concentration of 25 mM to 1000 mM.

#### *PRINCIPLES OF LAW*

It is well settled that “the discovery of an optimum value of a variable in a known process is usually obvious.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007). The rationale for determining the optimal parameters for prior art result effective variables “flows from the ‘normal desire of scientists or artisans to improve upon what is already generally known.’” *Id.* (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed.Cir.2003)).

Also, recently addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 U.S.C. § 103 “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Court further advised that “[a] person of ordinary skill is . . . a person of ordinary creativity, not an automaton.” *Id.* at 1742.

Regarding hindsight reasoning, the Court stated that “[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it.” *Id.* at 1742-1743 (citations omitted).

The Court further noted that a claim must be considered *prima facie* obvious when the prior art suggests its practice, even if the prior art’s reason for practicing the claimed subject matter is different than the applicant’s. *Id.* at 1741-1742 (“In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103.”).

#### *ANALYSIS*

We do not agree with Appellants that the Examiner erred in concluding that a person of ordinary skill in the art would have considered claim 31 *prima facie* obvious in view of Rothberg and Davidson. Rather, we agree with the Examiner that a person of ordinary skill practicing Rothberg’s h/l hybridization method (*see* FF 5-7), would have been prompted by the “normal desire of scientists or artisans to improve upon what is already generally known,” *In re Peterson*, 315 F.3d at 1330, to determine the optimal concentrations of DTT in Rothberg’s process.

One of ordinary skill in the art, being a person of ordinary creativity and common sense, *see KSR*, 1272 Sup. Ct. at 1742-43, would have reasonably inferred from the presence of DTT in Rothberg’s hybridization solution that changing the DTT concentration would affect the result of the

hybridization reaction. Thus recognizing the DTT concentration as a result-effective parameter, one of ordinary skill would have been prompted to ascertain the optimal concentration of that reactant.

We therefore do not agree with Appellants that Rothberg alone or in combination with Davidson would have failed to suggest that DTT was a result-effective parameter. Nor do we agree with Appellants that Rothberg only uses DTT in its ligation solutions, to the exclusion of the hybridization solutions. Moreover, as discussed above, Davidson expressly teaches that antioxidants retard photobleaching and therefore persons of skill in the art would have had reason to vary their concentration to achieve optimal levels of inhibition (FF 8).

Rothberg states that in the hybridization/ligation method “[p]referably, the ligase is in the [hybridization] solution and ligation occurs simultaneously with hybridization” (Rothberg, col. 61, ll. 39-41 (FF 5)). Rothberg describes the buffer for the “h/l” method by stating that “[t]ypically, hybridization occurs in a total volume of 10  $\mu$ l (placed over a UDA of 1.8 cm X 1.8 cm size and covered by a cover slip) of a solution containing 1 pM of target nucleic acids, 10% PEG ( $M_w$  6000), 66 mM Tris.Cl, 6.6 mM MgCl<sub>2</sub>, 10 mM DTT, 1 mM ATP and 40 mM NaCl (pH 7.5) at 25° C. for 80 min” (Rothberg, col. 61, ll. 30-35 (FF 7) (emphasis added)). The fact that Rothberg may elsewhere disclose other hybridization methods that lack DTT does not negate the fact that this embodiment of the “h/l” method uses DTT in its hybridization solution.

Appellants argue that because Rothberg uses DTT in the ligation reaction rather than the hybridization reaction, “optimization would only lead to optimizing the DTT concentration relative to the ligation step,” rather

than optimizing the inhibition of oxidizing the fluorescent dye (Reply Br. 10). However, claim 31 is not rendered non-obvious merely because a person of ordinary skill would have arrived at the claimed concentration of DTT for a reason different than Appellants' stated purpose of inhibiting oxidation of the fluorescent label. *See KSR*, 127 Sup. Ct. at 1741-1742 ("In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103.").

With respect to Appellants' argument that the combination of Rothberg and Davidson fails to suggest claim 31's process (App. Br. 8), we note that the Examiner did not rely on Davidson as suggesting any modification of Rothberg, but instead cited Davidson as evidence of fluorescent dyes' sensitivity to oxidation (*see* Ans. 4). For the reasons discussed above, we agree with the Examiner that a person of ordinary skill would have considered claim 31's process *prima facie* obvious in view of Rothberg.

Therefore, because Appellants do not assert, nor is it apparent, that any results coming from claim 31's process would have been considered unexpected by one of ordinary skill in the art, we affirm the Examiner's rejection of claim 31 as obvious over Rothberg and Davidson.

#### OBVIOUSNESS -- CLAIM 34

##### *ISSUE*

Claim 34 stands rejected under 35 U.S.C. § 103(a) as being obvious in view of Rothberg, as evidenced by Davidson, the Dictionary of Organic Compounds, and Winterbourn (Ans. 7-8).

The Examiner concedes that “Rothberg et al. do not teach mercapto-containing compounds comprising 2-mercaptoethylamine, N-acetylcysteine, an ovoidiol or a 4-mercaptoimidazole” (*id.* at 7). The Examiner nonetheless contends that “it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used [the] N-acetylcysteine of Winterbourn et al. in the method of Rothberg et al. since N-acetylcysteine is an antioxidant equivalent to DTT” (*id.*)

Appellants contend that because Rothberg does not disclose or suggest that its DTT-containing hybridization solution contains sufficient antioxidant to inhibit the oxidation of the fluorescent label, the cited combination of references fails to meet all of the claimed limitations, and therefore cannot render claim 34 obvious (App. Br. 8-9). Appellants further contend that one of ordinary skill in the art would not have been motivated to substitute Winterbourn’s compounds for Rothberg’s DTT (*id.* at 9).

The issue with respect to this rejection, therefore, is whether Appellants have shown that the Examiner erred in concluding that one of ordinary skill would have considered claim 34 obvious in view of Rothberg, Davidson, the Dictionary of Organic Compounds, and Winterbourn.

#### *FINDINGS OF FACT*

10. Claim 34 recites “[t]he method of claim 33, wherein the mercapto-containing compound comprises a member of the group consisting of 2-mercaptoethylamine, a thiol N-acetylcysteine, an ovoidiol, and a 4-mercaptoimidazole.”

Claim 33 recites “[t]he method of claim 28, wherein the antioxidant comprises a mercapto-containing compound.”

11. Winterbourn discloses that “[r]educed glutathione is the most abundant intracellular low molecular weight thiol, but other thiols can also protect against oxidative injury or inhibit signal transduction” (Winterbourn 322). Winterbourn studied the reactivity of the oxidants superoxide and hydrogen peroxide with a number of thiol compounds, including DTT and N-acetylcysteine (*see id.*, abstract). Winterbourn discloses that both DTT and N-acetylcysteine react with superoxide and hydrogen peroxide (*id.*, abstract; *see also* 323 (Figure 1) and 324 (Figure 2)).

#### *PRINCIPLES OF LAW*

Recently addressing the issue of obviousness, the Supreme Court reaffirmed that it is obvious to choose from among known equivalent solutions to a problem:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

*KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007).

“Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious.” *In re Fout*, 675 F.2d 297, 301 (CCPA 1982); *see also In re Mayne*, 104 F.3d 1339, 1340 (Fed. Cir. 1997) (“Because the applicants merely substituted one element known in the art for a known equivalent, this court affirms [the rejection for obviousness].”).

*ANALYSIS*

We agree with the Examiner that one of ordinary skill in the art using Rothberg's DTT-containing hybridization solution (*see* FF 5-7) would have reasoned that N-acetylcysteine would have been equivalently useful to DTT in Rothberg's hybridization. A person of ordinary skill would have recognized from Winterbourn that, in addition to being a thiol compound like DTT, N-acetylcysteine reacted with the same highly reactive superoxide and hydrogen peroxide species (FF 11). Thus recognizing the equivalent antioxidant effects of DTT and N-acetylcysteine, a person of ordinary skill would have been prompted to substitute Winterbourn's N-acetylcysteine for the DTT used in Rothberg's hybridization solution. We therefore agree with the Examiner that claim 34 would have been *prima facie* obvious to a person of ordinary skill in the art.

Appellants' argument, that the combination of references fails to meet all of the claimed limitations (App. Br. 8-9), does not persuade us that the Examiner erred in concluding that claim 34 would have been obvious to one of ordinary skill in the art. As discussed above, we agree with the Examiner that the amount of DTT used by Rothberg meets claim 28's, and therefore claim 34's, limitation requiring an antioxidant amount "sufficient to inhibit oxidation of the fluorescent label under the hybridization conditions."

Thus, one of ordinary skill in the art prompted by Winterbourn's disclosure of the equivalency of N-acetylcysteine and DTT to substitute N-acetylcysteine for DTT would have been further prompted to ensure that the equivalent amount of N-acetylcysteine was in Rothberg's hybridization solution. Moreover, because "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution

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obvious,” *In re Fout*, 675 F.2d at 301, we are not persuaded by Appellants’ argument regarding a lack of motivation for substituting Winterbourn’s N-acetylcysteine for Rothberg’s DTT.

#### SUMMARY

We affirm the Examiner’s rejection of claims 28-30, 32, and 33 under 35 U.S.C. § 102(e) as anticipated by Rothberg, as evidenced by Davidson and the Dictionary of Organic Compounds.

We affirm the Examiner’s rejection of claim 31 under 35 U.S.C. § 103(a) as obvious in view of Rothberg as evidenced by Davidson.

We affirm the Examiner’s rejection of claim 34 under 35 U.S.C. § 103(a) as obvious in view of Rothberg, as evidenced by Davidson, the Dictionary of Organic Compounds, and Winterbourn.

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

AFFIRMED

dm

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