The opinion in support of the decision being entered today was not written
for publication and is not binding precedent of the Board.

Paper No. 19

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte GRAHAM KEITH DIXON,
PETER MICHAEL BROAD and DAVID JOHN SCANLON

Appeal No. 2002-1367
Application No. 08/981,964

ON BRIEF

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

Opinion by GREEN, Administrative Patent Judge.
Dissenting opinion by GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-12. Claims 1 and 7 are representative of the subject matter on appeal, and read as follows:

> 1. A method for the identification of agents which inhibit sterol biosynthesis which method comprises contacting a test compound with a host cell comprising a DNA sequence which controls expression of a fungal acetoacetyl CoA thiolase gene operably linked to a reporter system such that modulation of sterol biosynthesis in the host cell leads to a detectable change in cell

phenotype, and determining whether any such detectable change has occurred.

7. A host cell which is a fungus transformed with a promoter element which controls expression of a fungal acetoacetyl CoA thiolase gene operably linked to a reporter system such that inhibition of sterol biosynthesis in the host cell leads to a detectable change in cell phenotype.

The examiner relies upon the following references:

Kirsch et al. (Kirsch) EP 0627491 Dec. 7, 1994

Servouse et al. (Servouse), "Regulation of Early Enzymes of Ergosterol Biosynthesis in Saccharomyces cerevisiae," Biochem. J., Vol. 240, pp. 541-47 (1986)

Dequin et al. (Dequin), "Cloning, Sequencing and Analysis of the Yeast S. uvarum ERG10 Gene Encoding Acetoacetyl CoA Thiolase," Curr. Genet., Vol. 13, pp. 471-78 (1988)

Hiser et al. (Hiser), "ERG10 from Saccharomyces cerevisiae Encodes Acetoacetyl-CoA Thiolase," J. Biol. Chem., Vol. 269, No. 50, pp. 31383-389 (1994)

Dimster-Denk et al. (Dimster-Denk), "Feedback regulation of 3-hydroxy-3-methylglutaryl Coenzyme A reductase in Saccharomyces cerevisiae," Molecular Biology of the Cell, Vol. 5, pp. 655-665 (1994)

Claims 1-12 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Kirsch, Servouse, and Dequin or Hiser. After careful review of the record and consideration of the issue before us, we reverse.

DISCUSSION

Claims 1-12 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Kirsch, Servouse, and Dequin or Hiser.

Kirsch is cited for describing a method for identifying sterol biosynthesis inhibitors wherein a test compound is contacted with a host cell transformed with a reporter construct. The rejection acknowledges that the methods of Kirsch "differ from those claimed . . . only in that the sterol biosynthetic gene promoter of the methods of Kirsch is that of the lanosterol 12-α-demethylase gene while the promoter of the reporter construct of the claimed methods is that of the acetoacetyl-CoA thiolase gene." Examiner's Answer, page 4.

Servouse is cited by the rejection for teaching

> that acetoacetyl-CoA thiolase is the first enzyme of the ergosterol biosynthesis pathway of yeast, that the activity of this enzyme is induced by ergosterol starvation and repressed by ergosterol excess and that the depression of activity in the presence of excess sterol is likely due to reduced enzyme synthesis since there is no detectable in vitro inhibition by ergosterol. As such one of ordinary skill in the art would have reasonably expected that regulation of acetoacetyl-CoA thiolase activity occurs at least in part by regulation of the transcription of the acetoacetyl-CoA thiolase gene.

Id. at 4-5.

Dequin and Hiser are cited for teaching the nucleic acid sequence from Saccharomyces encoding the acetoacetyl-CoA thiolase gene "which includes in each case several hundred nucleotides of the region 5' to the coding sequence of the gene which would be reasonably expected to contain the sequences necessary for regulation of transcription of the gene." Id. at 5.

The rejection concludes:

> Therefore, it would have been obvious to one of ordinary skill in the art to replace the lanosterol 14-α-demethylase gene

> promoter of the constructs of Kirsch [ ] with the 5' upstream region of the acetoacetyl-CoA thiolase gene of Dequin [ ] or Hiser [ ] in order to find inhibitors of sterol biosynthesis at any point along the biosynthesis pathway as acetoacetyl-CoA thiolase is the first enzymes [sic] of the sterol biosynthesis pathway.

Id. at 5.

Appellants argue that while Kirsch teaches a method for screening for sterol biosynthesis inhibitors based on the induction of lanosterol 14-α-demethylase, there is no suggestion of using another gene, such as the gene encoding the acetoacetyl-CoA thiolase enzyme, in the method. Appellants contend that "there is no teaching or suggestion in the cited references that feedback regulation occurred at least in part by regulation of transcription. Such a conclusion is apparently made with hindsight reconstruction of Appellants' invention using the teachings of their own specification." Appeal Brief, pages 5-6 (emphasis in original). Appellants argue further that "there does not appear to be any teaching or suggestion in the cited references that it would have been desirable to substitute the ACoAT gene promoter for the lanosterol 14-α-demethylase gene promoter used by Kirsch [ ] at the time Appellants' invention was made." Appeal Brief, page 7. We agree.

"A rejection based on section 103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, all facts must be considered. The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to

speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis. To the extent the Patent Office rulings are so supported, there is no basis for resolving doubts against their correctness. Likewise, we may not resolve doubts in favor of the Patent Office determination when there are deficiencies in the record as to the necessary factual bases supporting its legal conclusion of obviousness." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. Denied, 389 U.S. 1057 (1968) (emphasis in original).

As noted by the rejection, Servouse teaches that that acetoacetyl-CoA thiolase is the first enzyme of the ergosterol biosynthesis pathway of yeast, and that the activity of this enzyme is induced by ergosterol starvation and repressed by ergosterol excess. Servouse conjectures that "[e]nzyme depression is very likely due to reduced enzyme synthesis, since we . . . have been unable to detect feedback inhibition by ergosterol in vitro." Servouse, page 546, column 1.

With respect to Servouse, appellants assert that Servouse did not analyze mRNA or protein levels, "[t]herefore, it would have been a matter of pure speculation to hypothesize that regulation of sterol biosynthesis was at the level of transcription, translation, or some combination involving transcription and translation." Appeal Brief, page 4. Appellants argue further that at the time of the invention, little was known about the acetoacetyl-CoA thiolase (ACoAT) enzyme and its regulation. According to appellants, the enzyme may have been

subject to feedback regulation at the level of enzyme activity, or subject to feedback regulation at the level of the amount of protein. See id. at 5.

Appellants argue further that:

> [C]ontrary to the Examiner's assertion that feedback regulation would occur at least in part by regulation of transcription, there is no teaching or suggestion cited by the Examiner that would show that a person of ordinary skill in the art would have reasonably believed that the ACoAT gene promoter was able to confer sterol responsiveness when operably linked to a reporter system. As discussed above, even if control at the level of enzyme activity was discarded as a possibility, there is no evidence that a person of ordinary skill in the art would conclude that control was at the level of promoter-regulated transcription instead of controlling steps like protein degradation, degradation of RNA transcripts, splicing of transcripts to produce mRNA, transport of RNA or mRNA from nucleus to cytoplasm, assembly of ribosomes on mRNA, or translation of mRNA by ribosomes to produce protein.

Id. at 7.

The examiner responds by contending that:

> [O]ne of ordinary skill in the art would reasonably expect that an if an [sic] enzyme is regulated at the level of protein synthesis that this regulation would be effected at least in part by regulation of gene transcription as gene transcription is the first step in the protein synthesis pathway and regulation of the first step of a pathway is in most cases the most efficient means of accomplishing regulation without unnecessarily expending cellular resources (i.e., gene transcription utilizes large amounts of both energy resources and metabolic resources which would be wasted if the transcript was not then translated). While examples of all of the various means of regulating protein levels can be found in nature, regulation of transcription is by far the most commonly found means of doing this and in fact is the way mammalian cells regulate sterol biosynthesis. While as appellants note mammalian cells are often very wasteful of resources in order to maintain flexibility, fungi are not mammalian cells and wasteful use of resources is less common in lower eukaryotes and bacteria where such resources are likely to be in short supply. Furthermore, one

> of ordinary skill in the art would have been aware that many biosynthetic pathways are regulated by several different means (for example, both transcription and translational regulation may be found) as this provides additional flexibility at a lower cost in resources. For all of these reasons one of ordinary skill in the art would have reasonably expected in view of the teachings of Servouse [ ] that fungal ergosterol biosynthesis is regulated by the control of the amount of acetoacetyl-CoA thiolase in the cell and this regulation would be effected at least in part by regulation of gene transcription of the acetoacetyl-CoA thiolase gene.

Examiner's Answer, pages 7-8.

The above response as to why one of ordinary skill in the art would have expected that regulation of acetoacetyl-CoA thiolase amounts in a cell is accomplished, at least in part, by regulation of gene transcription, is a conclusion of the examiner that is not supported by any evidence in the record. "Conclusory statements," however, as to teaching, suggestion or motivation to arrive at the claimed invention "do not adequately address the issue" of obviousness. See In re Lee, 277 F.3d 1338, 1343-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002). Moreover, appellants cite the Dimster-Denk reference, see Appeal Brief, page 9, which teaches that regulation of the enzyme 3-hydroxy-3-methylglutaryl coenzyme reductase in S. cerevisiae, which is involved in isoprenoid synthesis, is at the level of translation, and not at the level of transcription. Appellants have thus made of record evidence that one of ordinary skill would not have necessarily expected enzyme regulation to occur at the level of transcription.

Because the examiner has not provided evidence to support the conclusion that one of ordinary skill in the art would have reasonably expected

that regulation of the acetoacetyl-CoA thiolase gene occurs at the level of gene transcription, the examiner has not met the burden of setting forth a prima facie case of obviousness, and the rejection is reversed.

We agree with our colleague in dissent that the issue before us on appeal was very close. We do not agree however, that the Servouse reference tips the scales and demonstrates that one of ordinary skill in the art would have expected the regulation of ACoAT expression to be carried out at the level of transcription.

First, with respect to Kirsch, that reference teaches "[a] method for screening for sterol biosynthesis inhibitors . . . by the induction of lanosterol 14-α-demethylase, an enzyme in the biosynthetic pathway of ergosterol and cholesterol." Kirsch, Abstract. Notably, Kirsch does not teach or suggest that other enzymes that are part of the biosynthetic pathway of ergosterol would be useful in the method.

As Hiser and Dequin are merely cited for teaching the nucleic acid sequence from Saccharomyces encoding the acetoacetyl-CoA thiolase gene and surrounding sequences, the focus falls on the Servouse reference to determine if that reference provides sufficient motivation to use the acetoacetyl-CoA thiolase gene in place of the lanosterol 14-α-demethylase in the method of Kirsch.

The dissent finds, based on the dictionary definitions of "repressing" and "inducing," that Servouse "provides sufficient evidence to show that those of skill in the art would have considered transcriptional regulation of ACoAT expression to be more likely than translational regulation." As noted by appellants, however,

Servouse measured a reduction of enzyme activity, with no analysis of mRNA or protein levels. See Reply Brief, page 3-4. The question thus becomes that, based on the evidence provided on the record, would the ordinary artisan conclude that acetoacetyl-CoA thiolase is regulated at the level of transcription. The examiner bases her conclusion on conclusory evidence, and the dissent bases his conclusion on the interpretation of “repressing” and “inducing.” The Dimster-Denk reference, however, was provided by appellants to demonstrate that enzyme regulation may occur in ways other than transcription. As it is the burden of the office to demonstrate unpatentability by the preponderance of the evidence, and as appellants have provided evidence to demonstrate that enzyme regulation may occur at levels other than transcription, we find that the evidence of record does not support the obviousness rejection.

CONCLUSION

Because the rejection fails to set forth a prima facie case of obviousness, it is reversed.

REVERSED

Demetra J. Mills Administrative Patent Judge	)) BOARD OF PATENT)) APPEALS AND)
Lora M. Green Administrative Patent Judge	) INTERFERENCES)

GRIMES, Administrative Patent Judge, dissenting.

The issue in this case—whether a preponderance of the evidence supports the examiner's rejection—is a close one, and certainly, the examiner's position would have been stronger if she had cited evidence showing that most yeast genes are regulated at the level of transcription, not translation. Nevertheless, I believe that a preponderance of the evidence supports the rejection, and I would affirm it.

The claims on appeal define a method for identifying inhibitors of sterol biosynthesis, by contacting a test compound with a host cell having within it a reporter gene linked to "a DNA sequence which controls expression of a fungal acetoacetyl CoA thiolase gene," and monitoring the expression of the reporter gene as a measure of sterol synthesis inhibition. See claim 1.

The examiner's primary reference, Kirsch, discloses a similar screening method, but using a reporter gene under the control of the lanosterol 14-α-demethylase gene rather than the acetoacetyl-CoA thiolase (ACoAT) gene. The other references cited by the examiner disclose the fungal ACoAT gene and surrounding sequences (Hiser and Dequin) and disclose that ACoAT is regulated in response to changes in ergosterol levels (Servouse).

As I understand their arguments, Appellants do not dispute that the elements needed to practice the claimed method (reporter genes, ACoAT gene sequences, and sterol biosynthesis inhibition assays) were known in the art. The critical issue, then, is whether a person of ordinary skill in the art would have

been motivated to replace the lanosterol 14-α-demethylase gene used by Kirsch with the ACoAT gene disclosed by Hiser or Dequin. The question of motivation, in turn, depends on whether a person of ordinary skill in the art would have expected that the ergosterol-induced inhibition of ACoAT observed by Servouse was a result of decreased transcription, or instead was a result of regulation at the level of protein translation or enzyme activity.

This last possibility can be discarded quickly. Servouse discloses that ACoAT "[e]nzyme depression is very likely due to reduced enzyme synthesis, since we and Trocha and Sprinson have been unable to detect feedback inhibition by ergosterol in vitro." Page 546. Thus, those of skill in the art would not have expected ergosterol to act directly on the ACoAT enzyme itself.

That leaves two possibilities: either ergosterol decreases ACoAT levels by inhibiting transcription, or it decreases ACoAT levels by inhibiting translation. What evidence of record favors each mechanism?

Appellants have provided evidence that another gene in the yeast sterol synthesis pathway is regulated at the translational level. Specifically, Dimster-Denk shows that mevalonate inhibits expression of the enzyme HMG-CoA reductase in yeast, and that the regulation is carried out at the level of translation. See the abstract. Appellants argue that Dimster-Denk "clearly contradicts the Examiner's assertion that a reduction in enzyme synthesis would be reasonably expected to arise by regulation of gene transcription." Appeal

Brief, page 9. More particularly, "Appellants do not contend that the person of ordinary skill in the art would therefore assume that transcriptional regulation was unlikely, but merely that regulation of gene expression is no more likely to be via transcription than not." Reply Brief, page 7 (emphasis added).

Thus, as I understand it, Appellants' argument is that Kirsch provides an example of a yeast sterol synthesis gene that is regulated by ergosterol at the level of transcription, while Dimster-Denk provides a counter-example of a yeast sterol synthesis gene that is regulated at the level of translation. Since Servouse provides no data to distinguish between the possibilities, the argument seems to go, the evidence is in equipoise; the examiner's rejection is not supported by a preponderance of the evidence.

The examiner provides the converse of Appellants' argument: although Dimster-Denk shows that HMG-CoA reductase is regulated at the translational level,

> this is balanced by the disclosure of Kirsch et al[.] which shows that Saccharomyces cerevisiae lanosterol 14-α-demethylase (also another enzyme in the ergosterol biosynthetic pathway) is clearly regulated at the transcriptional level. As such[,] one of ordinary skill in the art would not have believed that transcriptional regulation of sterol biosynthetic genes in yeast was unlikely.

Examiner's Answer, pages 9-10. The examiner argues that those skilled in the art would have considered transcriptional regulation more likely because it is more common and more efficient. See id., pages 7-8. Unfortunately, as the majority points out, the examiner did not cite any evidence to support these assertions.

Although I do not agree completely with the examiner's rationale, I do agree with her conclusion. I believe Servouse provides sufficient evidence to tip the balance of the evidence in the examiner's favor. First, Servouse states consistently that the experimental data suggest that ergosterol "represses" ACoAT, or to state it a different way, an absence of ergosterol "induces" ACoAT. See the following passages:

- "These results show that ergosterol could regulate its own synthesis, at least partially, by repression of the first two enzymes of the pathway [ACoAT and HMG-CoA synthase]." Abstract (emphasis added).
- "From these observations, it can be concluded that ergosterol starvation induces thiolase and synthase activities. Conversely, ergosterol excess would repress the same enzyme activities." Page 546, left-hand column (emphasis added).
- "[I]n anaerobically grown cells where membranous systems are poorly developed, sterol molecules (ergosterol or cholesterol . . .) could enter the cell nucleus and repress enzyme synthesis." Page 546, right-hand column (emphasis added).

My dictionary defines "repress" to mean, among other things, "to inactivate (a gene or formation of a gene product) by allosteric combination at a DNA binding site"; it defines "inducer" to mean "one that induces; especially: a substance that is capable of activating a structural gene by combining with and inactivating a genetic repressor." Merriam-Webster's Collegiate Dictionary, Deluxe Edition (1998) (copies attached). These dictionary definitions show that "repressing" and "inducing", as used in the field of molecular biology, are understood to refer to regulation of gene transcription.

As Appellants concede, contemporaneous publications are evidence of the understanding and expectations of those of ordinary skill in the art. See the Appeal Brief, page 8 ("[S]cientific publications are evidence of what a person of ordinary skill in the art would have expected when Appellants' invention was made."). Thus, Servouse provides evidence that those skilled in the art expected the regulation of ACoAT expression to be carried out at the level of transcription.

In addition, Servouse provides evidence to show that ACoAT is regulated differently from the HMG-CoA reductase that Appellants rely on as an example of translational regulation. Servouse states that:

- "Measurements of the specific activities of acetoacetyl-CoA thiolase, HMG-CoA . . . synthase and HMG-CoA reductase (the first three enzymes of the pathway), show that in cells deprived of ergosterol, acetoacetyl-CoA thiolase and HMG-CoA synthase are generally increased. In an excess of ergosterol, in anaerobiosis, the same enzymes are strongly decreased. . . . <u>In contrast, HMG-CoA reductase is only slightly affected by these conditions</u>." Abstract (emphasis added).
- "The results show that acetoacetyl-CoA thiolase activity presents the greatest change according to culture conditions, HMG-CoA reductase activity being only slightly modified." Page 541, right-hand column.
- "[T]hese results also strongly suggest that ergosterol may play a role in the regulation of its biosynthesis, in particular by regulating acetoacetyl-CoA thiolase and HMG-CoA synthase rather than HMG-CoA reductase." Page 546, left-hand column.

The disclosure that ACoAT is regulated differently from HMG-CoA reductase is evidence that would have led those skilled in the art to discount the possibility that ACoAT, like HMG-CoA reductase, is regulated at the translational level.

Granted, Servouse does not show definitively that ACoAT is regulated at the level of transcription. That, however, is not required. Proving a fact by a preponderance of the evidence requires only "evidence which is of greater weight or more convincing than the evidence which is offered in opposition to it; that is, evidence which as a whole shows that the fact sought to be proved is more probable than not." Black's Law Dictionary, 6th edition (1990).

Here, there are apparently only two possible mechanisms of regulation to distinguish between, and Servouse provides evidence that those skilled in the art considered transcriptional regulation to be more likely than translational regulation. Thus, in my view, Servouse provides sufficient evidence to show that those of skill in the art would have expected ACoAT expression to be, more likely than not, regulated at the level of transcription. I believe the examiner's rejection is supported by a preponderance of the evidence.

My colleagues on this panel conclude that the examiner has not made out a prima facie case. I find it hard to fault the majority's analysis, as far as it goes: the examiner bears the initial burden of showing unpatentability by a preponderance of the evidence; the examiner here did not provide the evidence needed to support the rationale she relied on; therefore, the rejection as presented on appeal does not show prima facie obviousness and we can in good faith reverse it.

While there is nothing wrong with the majority's analysis, I believe that in a case like this one, where the evidence shows more than the examiner says, we

should consider the evidence for what it shows, not for how it is characterized. No injustice is done by our considering and applying the full disclosures of the references; Appellants have had a full and fair opportunity to consider the references and to respond to the rejection as they consider best.

In addition, the public interest is best served by ensuring that patents issue only when they meet the statutory requirements. If we conclude, as I do here, that the examiner has relied on references that could support a case of unpatentability, but has made out what is not quite a legally sufficient case, we should try to ensure that the end result—issuance or nonissuance of a patent—comports with the statutory mandate.

I realize that our role is to review decisions made by examiners, not to examine patent applications ourselves. We are not, therefore, required to go beyond the grounds of rejection presented by the examiner. We are not required to, but in a case like this, we should. I would affirm the rejection.

	) BOARD OF PATENT
	)
Eric Grimes	) APPEALS AND
Administrative Patent Judge	)
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