

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

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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*Ex parte* JOSEF ALTENBUCHNER, ANDREAS BOMMARIUS, RALF  
MATTES, CHRISTOPH SYLDATK, WILHELM TISCHER,  
ANJA WIESE, and BURKARD WILMS

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Appeal 2007-1069  
Application 10/334,990  
Technology Center 1600

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Decided: June 15, 2007

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Before DONALD E. ADAMS, DEMETRA J. MILLS, and RICHARD M.  
LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

**DECISION ON APPEAL**

This is a decision on appeal from the final rejection of claims 17-19, 21-24, 26-28, 30-38, and 41-46. We have jurisdiction under 35 U.S.C. § 6(b). We reverse the rejections under 35 U.S.C. § 112, first and second paragraphs and § 103, but affirm the rejection for nonstatutory obvious-type double-patenting.

## STATEMENT OF CASE

*Arthrobacter aurescens* DSM 3747 is one of the few isolated microorganisms capable of converting 5-monosubstituted hydantoins to L-amino acids. The disadvantage of using *A. aurescens* cells as [a] biocatalyst is the low enzyme activity. Especially the L-N-carbamoylase is the bottleneck for most substrates leading to an increase of the intermediate L-N-carbamoyl amino acid in the cell, which is not further converted to the corresponding amino acid.

(Specification 1: 28 to 2: 3.)

The asymmetric bio-conversion to either L- or D- amino acids involves three enzymes: hydantoinase, hydantoin racemase, and D- or L-specific carbamoylase (Specification 1: 19-27; 2: 8-16). The claimed invention is directed to microorganisms (“whole cell catalysts”) transformed with DNAs coding for hydantoinase, hydantoin racemase, and carbamoylase, and methods of using the microorganisms to produce enantiomerically enriched amino acids.

Using whole cell catalysts comprising cloned genes encoding for a hydantoinase, for a hydantoin racemase and a D- or L-specific carbamoylase for the conversion of 5-monosubstituted hydantoins to L- or D-amino acids results in a fast and complete conversion of racemic mixtures of hydantoins to the corresponding L- or D-amino acids on industrial scale. This significantly reduces the production costs due to a reduction of fermentation and purification costs because all enzymes are produced in one strain.

(Specification 3: 1-9.)

Claims 17-19, 21-24, 26-28, 30-38, and 41-46 are on appeal (Br. 4). Claims 39 and 40 have been allowed (Br. 4). The appealed claims stand rejected under 35 U.S.C. § 112, first and second paragraphs, 35 U.S.C. § 103(a), and nonstatutory obvious-type double-patenting (Br. 9).

The Examiner relies on the following as evidence of unpatentability:

Wagner      US 5,827,717      Oct. 27, 1998

Van de Loo, *Proc. Natl. Acad. Sci.*, 92: 6743-6747 (1995).

Broun, *Science*, 282: 1315-1327 (1998).

Bork, *Genome Research*, 10:498-400 (2000).

We select claim 17, the broadest and only independent claim on appeal, as representative:

17. A microorganism which
  - (A) is transformed with DNAs encoding (i) a hydantoinase, (ii) a hydantoin racemase, and (iii) a D- or L-specific carbamoylase, and
  - (B) converts 5-monosubstituted hydantoins to L- or D-amino acids,wherein the DNAs encoding the hydantoinase, the hydantoin racemase, and the D- or L-specific carbamoylase are overexpressed in the microorganism according to the turnover rates of the respective enzymes to reduce the accumulation of intermediates in the conversion of the 5-monosubstituted hydantoins to L- or D-amino acids.

## DISCUSSION

### *Rejection under § 112, second paragraph*

Claims 17-19, 21-24, 26-28, 30-38, and 42-46 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite (Answer 3; Br. 9).

Claim 17 is directed to a microorganism transformed with DNAs encoding 1) hydantoinase, 2) hydantoin racemase, and 3) D- or L-specific carbamoylase. The DNAs are

overexpressed in the microorganism according to the turnover rates of the respective enzymes to reduce the accumulation of intermediates in the conversion of the 5-monosubstituted hydantoins to L- or D-amino acids.

The Examiner states the claimed phrase is indefinite because “there are many turnover rates for an enzyme” and “it is not clear which ‘turnover rates’ are being referred to or how they relate to overexpression” (Answer 3-4).

Claims are interpreted 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).

According to the Specification, enzymes “naturally possess different turnover rates”<sup>1</sup> (Specification 3: 23-24). When the turnover “rates of co-working enzymes are not in line . . . [,] intermediates accumulate . . . inside the cell” (Specification 3: 24-26). Overexpression can also lead to “the formation of inclusion bodies . . . which is unfavourable for a well balanced coexpression of all the three enzymes” (Specification 3: 26-30). “Therefore, various attempts to ‘fine tune’ the expression of these genes have been

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<sup>1</sup> “Turnover rate” refers to the number of substrate molecules in a certain time period that an enzyme can process. Bruce Alberts, *Molecular Biology of the Cell* 163 (4<sup>th</sup> Edition, 2002).

made. This can be done advantageously by overexpressing the hydantoinase genes in question according to their turnover rates” (Specification 3: 30-33).

Several different approaches are disclosed “[t]o adopt the turnover rate of all enzymes expressed in the whole cell” (Specification 5: 23-25), including by the use of different promoters, mutant enzymes, enzymes from different sources, and replicons (e.g., plasmids) with different copy numbers (Specification 5: 26 to 6: 29). Since “turnover rate” refers to the speed at which enzymes process their substrates, the amount of enzyme expressed in the cell determines how much substrate is processed in a given time period.

“The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.” *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993) (citations omitted).

In our opinion, the skilled worker would understand, in the context of the Specification, “the DNAs” are “overexpressed in the microorganism according to the turnover rates of the respective enzymes” means that the expression of the three different synthetic enzymes is adjusted to avoid accumulation of intermediates.

Fig. 5 shows that adjusting the expression of the enzymes according to their turnover rate avoids the accumulation of intermediate (“CaTrp”) when the substrate (“IMH”) is converted to the final product (“Trp”) (Specification 7: 24-30). In contrast, Fig. 6, in which the enzyme expression levels differ from those in the experiment illustrated in Fig. 5 (Specification

10 (Table 1)), shows an experiment which results in the accumulation of the intermediate (CaTrp) (Specification 7: 31 to 8: 3).

Because the Specification reasonably apprises those skilled in the art of the scope of the claimed invention, we conclude that the claims are in conformance with § 112, second paragraph. We reverse the rejection of claims 17-19, 21-24, 26-28, 30-38, and 42-46.

*Rejection under § 112, first paragraph, for lack of written description*

Claims 17-19, 21-24, 26-28, 30-38, 42, 45, and 46 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description of the claimed invention (Answer 4; Br. 9). The Examiner states that the claims are directed to “a microorganism transformed with a genus of DNAs encoding hydantoinases, hydantoin racemases, and/or carbamoylases, wherein all the DNAs can have any structure” (Answer 4). Relying on *University of California v. Eli Lilly and Co.* (“Lilly”), 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), the Examiner states that

the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus.

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In the instant case, *there is no structural limitation* recited with regard to *all* the members of the genus of polynucleotides recited.

(Answer 5.)

In our opinion, *Lilly* is not the proper standard to apply to the claims in this appeal. In *Lilly*, at issue was the written description of a novel DNA genus. *Lilly*, 119 F.3d at 1563, 1567, 43 USPQ2d at 1401, 1405. In this case, DNA sequences for the claimed enzymes were known in the prior art. It is unnecessary for a patent application to provide a description of nucleotide sequences which are already known in the prior art. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367, 79 USPQ2d 1001, 1008 (Fed. Cir. 2006). As explained in *Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 USPQ2d 1078, 1084-5 (Fed. Cir. 2005):

The “written description” requirement must be applied in the context of the particular invention and the state of the knowledge. The Board’s rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.

Here, the claimed enzymes – hydantoinase, hydantoin racemase, and D- or L-carbamoylase – were well-known and characterized in the prior art. As explained by Appellants, enzyme activities for each of the three enzyme classes were known in the art prior to the filing date of the application (Br. 13). Conserved amino acid motifs had been established for each enzyme class (Br. 16, 18, 20 (Tables 1-3)). Nucleotide information for these

enzymes was also known and could be deduced from the amino acid sequences based on the known genetic code (Br. 21). Like the circumstances in *Capon*, Appellants are not claiming to have discovered the DNAs recited in claim 17; they are prepared from known DNA sequences of known function. The Examiner erred in concluding that the Specification does not meet the written description requirement because it does not reiterate the structure of the claimed genus of known enzymes. We reverse the rejection of claims 17-19, 21-24, 26-28, 30-38, 42, 45, and 46 for lack of written description.

*Rejection under § 112, first paragraph for lack of enablement*

Claims 17-19, 21-24, 26-28, 30-38, 42, 45, and 46 stand rejected under § 112, first paragraph, for lack of enablement (Answer 8). The Examiner states that it would require undue experimentation to practice the claimed invention with “a microorganism transformed with a DNA encoding any hydantoinase, hydantoin racemase and/or carbamoylase” (Answer 8). The Examiner asserts “[t]he scope of the claims . . . is not commensurate with the enablement provided in regard to the extremely large number of unknown DNAs encoding any hydantoinase, hydantoin racemase, or carbamoylase required to practice the claimed invention” (Answer 8). The Examiner contends that the example of enzymes from one strain of *Arthobacter* (SEQ ID NOS: 8, 10, and 6) is not sufficient to enable the full scope of the claim because there is no information about the structure of other hydantoinases, hydantoin racemases, and carbamoylases (Answer 9). The Examiner also states that it would not be routine “to isolate/create any polynucleotide encoding a protein with the activity recited without any

knowledge as to the structural features which would correlate with that activity” (Answer 9).

“To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). The Examiner’s rejection is based on the breadth of the claimed genus in covering enzyme coding sequences which are not disclosed or described in the Specification. However, Appellants have provided evidence that the claimed enzymes – hydantoinase, hydantoin racemase and D- or L-specific carbamoylases – had been characterized in the prior art and that many examples of each enzyme type were known prior to the filing date of the application (Br. 12-21).

Appellants also present evidence that conserved amino acid motifs involved in enzyme catalysis were known for each enzyme class (Br. 14-20). While the Examiner acknowledges the existence of these conserved motifs, the Examiner contends that “it is unlikely that these small motifs [are] all that is required for a protein to have the recited enzymatic activity since the catalytic sites for enzymes are expected to be larger than 5 amino acids” (Answer 26). We do not find this persuasive. First, the catalytic regions of each enzyme class are not characterized as having less than 5 amino acids. For hydantoinases, conserved residues span almost 200 amino acids (e.g., from 56-239) (Br. 16); for hydantoinase racemase, more than nine amino acids (e.g., from 196-208; from 196-204) (Br. 18). Secondly, because a large number of enzymes were known in the prior, including their

identifying and functional characteristics, this would have aided the skilled person in the construction of additional enzymes within the claim scope.

We also find Appellant' arguments persuasive that it would not require undue experimentation to express the genus of claimed enzymes in bacteria, and use the bacteria to produce amino acids, because such methods were well known in the art at the time the application was filed. (Br. 24-26).

In sum, we conclude that a person of ordinary skill in the art would have clearly possessed sufficient knowledge to make and use the full scope of the claims. We reverse the rejection of claims 17-19, 21-24, 26-28, 30-38, 42, 45, and 46 as lacking enablement.

*Rejection under § 103*

Claims 17, 18, and 30 stand rejected under 35 U.S.C. § 103(a) as obvious over Wagner (Answer 10).

Wagner teaches microorganisms which are capable of converting 5-monosubstituted hydantoins or N-carbamoyl alpha amino acids into pure L-amino acids using a carbamoylase, hydantoinase, and hydantoin racemase (Wagner, col. 1, ll. 8-12; Answer 10). Wagner also describes obtaining a gene coding for a carbamoylase, hydantoinase, or hydantoin racemase (Wagner, col. 1, ll. 65-67). "As persons of ordinary skill would appreciate, these genes may be useful for" inserting into a microorganism to "produce large amounts of the enzyme(s)" (Wagner, col. 3, ll. 28-36).

In reaching an obviousness determination, it is necessary to identify the differences between the claimed invention and the prior art, and then to determine whether these differences are obvious in view of the scope and

content of the prior art and the level of skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 13-14, 148 USPQ 459, 465 (1966). The Examiner finds that Wagner teaches inserting a gene coding for a carbamoylase, hydantoinase, and/or hydantoin racemase, but does not teach “a microorganism transformed with a plasmid containing DNA encoding a carbamoylase, hydantoinase, and a hydantoin racemase, wherein said DNAs are expressed at rates which result in reduced accumulation of intermediates in the conversion of 5-monosubstituted hydantoins to L- or D-amino acids” as required by claim 17 (Answer 10). However, the Examiner concludes that the claimed expression method would have been obvious because

D- and L- amino acids are widely used biochemicals, therefore methods of making such amino acids are highly desirable. Also, one of skill in the art is motivated to express these genes at rates which would avoid accumulation of intermediates because accumulation of intermediates can potentially reduce yield and is not efficient.

(Answer 11).

The Examiner bears the initial burden of showing unpatentability. *See, e.g., In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). “[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (quoted in *KSR Int’l Co. v. Teleflex Inc.*, 127 S.Ct 1727, \_\_\_, 82 USPQ2d 1385, 1396 (2007)). Common knowledge and common sense are a part of this reasoning. *See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367, 80 USPQ2d 1641, 1650 (Fed.

Cir. 2006). However, in this case, the Examiner has only made conclusory statements, and has not presented sufficient evidence that a person of ordinary skill in the art would have known to overexpress hydantoinase, hydantoin racemase, and carbomoylase according to their turnover rates in order “to reduce the accumulation of intermediates in the conversion of the 5-monosubstituted hydantoins to L- or D-amino acids” as required by claim 17.

Wagner describes gene cloning and expression of cloned genes coding for amino acid producing enzymes (Wagner, col. 3, ll. 25-40), but does not disclose specific cloning or expression methods. Wagner also states that a “person of ordinary skill would appreciate” that the cloned genes could be used for expression purposes (Wagner, col. 3, ll. 28-32). Based on this evidence, it is reasonable to presume that expression methods were well-known in the art and that one of ordinary skill did not require explicit instructions on how to express genes.

Although the skilled worker was knowledgeable about cloning and expressing genes, and may have had reason to express all *three* genes in a single microorganism, the Examiner presents no evidence that the skilled worker would have known to overexpress the genes “according to the[ir] turnover rates . . . to reduce the accumulation of intermediates in the conversion of the 5-monosubstituted hydantoins to L- or D-amino acids” as required by claim 17. The Examiner states that “accumulation of intermediates can potentially reduce yield and is not efficient” (Answer 11), but provides no support that this was common knowledge in this field.

Fig. 6 of the Specification shows that not all methods in which the three genes are co-expressed in a microorganism result in reducing intermediate accumulation (*see supra* on p. 5). In sum, there is nothing in the record that would lead us to believe that adjusting the co-expression levels according to “turnover rates” to reduce intermediate accumulation is an obvious solution to the problem of amino acid production addressed by Appellants’ claims.

For the foregoing reasons, we reverse the rejections of claims 17, 18, and 30 as obvious over Wagner.

*Rejection under nonstatutory obvious-type double-patenting*

Claims 17-19, 21-24, 26-28, 30-38, and 41-46 stand rejected on the ground of nonstatutory obvious-type double patenting over claims 1-56 of US 6,713,288 (Answer 12).

Appellants request that the rejection “be held in abeyance until the time allowable subject matter is identified” (Br. 27). Since Appellants have not disputed the merits of the rejection, we affirm it.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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