

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte STEPHEN B. H. KENT,
SASKIA C. F. MILTON, and
RAYMOND C. MILTON

Appeal No. 2001-0762
Application No. 08/343,585

ON BRIEF

Before WINTERS, ADAMS, and GREEN, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-8, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A synthetic D-enzyme corresponding to a natural L-enzyme, wherein the synthetic D-enzyme has a D-amino acid residue sequence consisting of D-amino acids and glycine that defines a D-polypeptide able to catalyze a first enzymatic reaction corresponding to a second enzymatic reaction catalyzed by the natural enzyme,
said D-amino acid residue sequence corresponding to an L-amino acid residue sequence defined by the natural L-enzyme,
said D-polypeptide having a conformation that corresponds to a mirror image of an L-polypeptide defined by the natural L-enzyme.

The references relied upon by the examiner are:

Flouret et al. (Flouret), "The synthesis of D-Oxytocin, the enantiomer of the posterior pituitary hormone, oxytocin," J. Am. Chem. Soc., Vol. 87, No. 16, pp. 3775-3776 (1965)

Stewart et al. (Stewart), "All-D-Bradykinin and the problem of peptide antimetabolites," Nature, Vol. 206, pp. 619-620 (1965)

Vogler et al. (Volger), "Synthese von All-D-Val⁵-Angioteinsin II-Asp¹-β-Amid¹," Fasciculus 6, Vol. 48, No. 152, pp.1407-1414 (1965)

Fassina et al. (Fassina), "Recognition properties of peptides hydrophatically complementary to residues 356-375 of the c-raf protein," J Biol. Chem., Vol. 264, No. 19, pp. 11252-11257 (1969)

Wlodawer et al. (Wlodawer), "Conserved folding in retroviral proteases: Crystal structure of a synthetic HIV – 1 protease," Science, Vol. 245, pp.616-621 (1989)

Zawadzke et al. (Zawadzke), "A Racemic Protein," J. Am. Chem. Soc., Vol. 114, pp. 4002-4003 (1989)

Bessalle et al. (Bessalle), "All-D-magainin: chirality, antimicrobial activity and proteolytic resistance," FEBS, Vol. 274, No. 1,2, pp.151-155 (1990)

Wade et al. (Wade), "All-D amino acid-containing channel-forming antibiotic peptides," Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 4761-4765 (1990)

The reference relied upon by appellants is:

Saint-Martin et al. (Saint-Martin), "Hydrogen production and deuterium-proton exchange reactions catalyzed by *Desulfovibrio nickel(II)*-substituted rubredoxins," Proc. Natl. Acad. Sci., USA, Vol. 85, pp. 9378-80 (1988)

GROUND OF REJECTION

Claims 1-8 stand rejected under 35 U.S.C. § 103 as being unpatentable over Zawadzke, Stewart, Wade, Vogler, Flouret, Fassina and Bessalle in view of Wlodawer.¹

¹ We note the examiner's reliance on Jung, "Proteins from the D-Chiral World," Angew. Chem. Int. Ed. Engl., Vol. 31, No. 11, pp. 1457-1459 (1992), and Petsko, "On the Other Hand . . .," Science, Vol. 256, pp. 1403-1404 (1992). Answer, page 18. These references, however, were

We reverse.

DISCUSSION

The examiner relies on Stewart, Wade, Vogler, Flouret, Fassina and Bessalle to teach D-proteins which include, inter alia, bradykinin, cecropin, angiotensin andoxytocin. Answer, pages 5-7. However, both the examiner (see id.) and appellants (Brief, pages 4-5) emphasize that these references do not teach D-enzymes.

The examiner relies on Wlodawer (Answer, page 7) to teach “the crystal structure of chemically synthesized HIV protease analog.” However, both the examiner (see id.) and appellants (Brief, page 5) recognize that Wlodawer does not disclose or suggest the crystal structure of synthetic D-HIV protease or reaction with D-substrates.

The claimed invention is drawn, inter alia, to a synthetic D-enzyme that is able to catalyze an enzymatic reaction that corresponds to a natural enzyme and

not included in the statement of the rejection. As set forth in In re Hoch, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n.3 (CCPA 1970), “[w]here a reference is relied on to support a rejection, whether or not in a ‘minor capacity,’ there would appear to be no excuse for not positively including the reference in the statement of the rejection”. Accordingly, we have not considered these references in our deliberation.

has a D-amino acid residue sequence corresponding to an L-amino acid residue sequence defined by the natural L-enzyme. As disclosed at page 14 of appellants' specification:

Many enzymes ... have been the subject of mutation of their natural amino acid residue sequence such that they no longer correspond in amino acid residue sequence to the sequence of a natural isolate, and yet still retain an enzymatic activity. Thus, in another embodiment, the invention contemplates D-enzymes having amino acid residue sequences that correspond to known enzymes.

Therefore, as we understand appellants' claimed invention, the sequence of the claimed enzyme must be the same as that of the natural enzyme but for the use of D-amino acids and glycine.

The only reference relied upon by the examiner that comes close to meeting the requirements of the claimed invention is Zawadzke. According to the examiner (Answer, page 5), Zawadzke teaches "the chemical synthesis of all-D-rubredoxin." The examiner notes (id.), "that the protein has a 'relatively high hydrogenase-like activity of its Ni²⁺ complex['] ... [and therefore] can be considered an honorary enzyme...." According to the examiner (id.), while Zawadzke does not teach the reaction of this D-enzyme with chiral substrates, the D-form of rubredoxin can be used "to solve the crystallographic phase problem."

In response, appellants argue (Brief, page 6) that while "Zawadzke cites a prior art reference (Saint Martin) which observes that a non-naturally occurring Ni²⁺ complex of the native L-rubredoxin has a 'hydrogenase-like activity' ... [Zawadzke] does not disclose or suggest that either of his synthetic D-[]or L-

rubredoxin analogs bind with Ni^{2+} to form a similar complex.” Appellants further explain (Answer, page 7), “although Zawadzke never made the Ni^{2+} complex of his rubredoxin analog, ... [Saint-Martin] have made the Ni^{2+} complex of various native rubredoxins, including rubredoxin isolated from D[.] desulfuricans ATCC 27774, i.e., the same rubredoxin after which Zawadzke modeled his analog....”

With regard to the rubredoxin isolate used by Zawadzke, appellants point out (Brief, page 8) that this rubredoxin isolate has “five cysteines, four of which participate in a ligation with Fe^{2+} or Fe^{3+} in the native state and one of which is non-ligating.” Appellants further explain (id.), “[w]hen synthesizing his rubredoxin analog, Zawadzke deletes the firth [sic] cysteine, ie., the non-ligating cysteine.”

The examiner recognizes that Zawadzke’s rubredoxin analog is different from Saint-Martin’s rubredoxin in that it lacks the native N-formyl group and the non-ligating cysteine was replaced with alanine. Answer, page 9. However, it is the examiner’s position (Answer, bridging sentence, pages 9-10) that these differences “are so minor that a person of ordinary skill in the art would reasonably be expected to interpret the disclosure of Zawadzke et al. as ‘corresponding’ to native rubredoxin.” In support of this position, the examiner finds (Answer, page 10), “the binding affinity of Fe^{3+} for the native and analog rubredoxins are the same within experimental error. Both the all-L and all-D analogs had the same binding affinity.” We note however, that Zawadzke is silent with regard to the effect these modifications had with respect to Ni^{2+}

binding, which is required to provide the protein with its “honorary” enzymatic activity. Nevertheless, the examiner asserts (id.)”

a person of ordinary skill in the art would reasonably expect that the all-D Ni²⁺ rubredoxin analog would exhibit the same hydrogenase-like activity discussed for the all-L Ni²⁺ rubredoxin in Zawadzke et al. (citing Saint-Martin ...) as a result of the binding of Ni²⁺ to the coordinating site in the same manner in either all-D or all-L rubredoxin.

However, as appellants point out, the facts in evidence dispute the examiner’s conclusion. According to appellants (Brief, page 8), Saint-Martin state “[a]t present it is difficult to establish a complete mechanism for hydrogen activation by the modified rubredoxins.” With regard to the rubredoxin isolate used by Zawadzke appellants argue that Saint-Martin state:

This rubredoxin has the peculiarity of having the shortest amino acid polypeptide chain (45 amino acids instead of the 53 of the other two) but has one more cysteine (5 cysteine residues instead of 4) ... These differences may be significant in the respective activities observed, but further experiments are necessary to assess the implication of these differences in the mechanism of activation of the hydrogen molecule by the modified Ni-rubredoxins.

To support prima facie case of obviousness, the prior art relied upon must provide a person of ordinary skill in the art with a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Based on the evidence of record, and in contrast to the examiner’s position, we are compelled to agree with appellants (Brief, page 9) that one of ordinary skill in the art at the time the invention was made would not have believed that the changes between the native and analog rubredoxins were minor with respect to its hydrogenase activity, or that it could be reasonably expected that Zawadzke’s modified rubredoxin would have had the hydrogenase

activity of the Ni²⁺ complex of the native protein. Stated differently, based on the evidence before us, it is our opinion that a person of ordinary skill in the art would not have had a reasonable expectation of success in obtaining a D-rubredoxin that exhibited hydrogenase-like activity.

Accordingly, we reverse the rejection of claims 1-8 under 35 U.S.C. § 103 as being unpatentable over Zawadzke, Stewart, Wade, Vogler, Flouret, Fassina and Bessalle in view of Wlodawer.

REVERSED

Sherman D. Winters)	
Administrative Patent Judge)	
)	
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)	BOARD OF PATENT
Donald E. Adams)	
Administrative Patent Judge)	APPEALS AND
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)	INTERFERENCES
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Lora M. Green)	
Administrative Patent Judge)	

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