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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ZHENG XIN DONG

Appeal 2011-010047
Application 10/546,303
Technology Center 1600

Before DONALD E. ADAMS, FRANCISCO C. PRATS, and
STEPHEN WALSH, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to analogues of glucagon-like peptide-1 (GLP-1). The Examiner entered a rejection for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

“In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus” (Spec. [004] (citation omitted)).

“GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. . . . This metabolic instability limits the therapeutic potential of native GLP-1” (*id.* at [006] (citation omitted)).

Accordingly, Appellant’s invention is directed to producing “GLP-1 analogues that are more active or are more metabolically stable than native GLP-1” (*id.*). The GLP-1 analogues are produced by substituting alternative moieties for the naturally occurring amino acids at various positions in the GLP-1 sequence (*see id.* at [007]-[0974]).

The Specification discloses that in “a most preferred embodiment” the GLP-1 analogue is (Ser⁸, Aib³⁵)hGLP-1(7-36)NH₂ (SEQ ID NO: 767) (*id.* at [0957]). As the Specification explains, this nomenclature indicates that the compound consists of amino acids 7 through 36 of the native peptide sequence of human GLP-1, with the C-terminus having been amidated, serine substituted at position 8 of the peptide sequence, and α -aminoisobutyric acid (Aib) substituted at position 35 of the sequence (*see id.* at [0974], [0958]).

Claims 15-18 stand rejected and appealed (*see App. Br.* 3-4). As Appellant did not argue the patentability of the claims separately, the claims stand or fall together. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 15 illustrates the appealed subject matter and reads as follows:

- 15: A compound wherein said compound is:
- | | |
|---|-----------------|
| (Ser ⁸ , Aib ³⁵)hGLP-1(7-36)NH ₂ ; | (SEQ ID NO.767) |
| (Abu ⁸ , β -Ala ³⁵)hGLP-1(7-36)NH ₂ ; | (SEQ ID NO.768) |
| (Val ⁸ , β -Ala ³⁵)hGLP-1(7-36)NH ₂ ; | (SEQ ID NO.769) |
| (β -Ala ^{8,35})hGLP-1(7-36)NH ₂ ; | (SEQ ID NO.770) |
| (Abu ⁸ , Aib ³⁵)hGLP-1(7-36)NH ₂ ; | (SEQ ID NO.771) |
| (Val ⁸ , Aib ³⁵)hGLP-1(7-36)NH ₂ ; | (SEQ ID NO.772) |
| or (β -Ala ⁸ , Aib ³⁵)hGLP-1(7-36)NH ₂ ; | (SEQ ID NO.773) |
- or a pharmaceutically acceptable salt thereof.

In response to a species election requirement, Appellant elected the preferred and first claimed compound, (Ser⁸, Aib³⁵)hGLP-1(7-36)NH₂ (SEQ ID NO: 767), for prosecution on the merits (*see* App. Br. 4). We therefore limit our analysis of claim 15 to the patentability of the elected compound, and the extent to which the claims read on it. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

The sole rejection before us for review is the Examiner's rejection of claims 15-18 under 35 U.S.C. § 103(a) as obvious over Dong¹ and Deacon² (Ans. 3-4).

OBVIOUSNESS

The Examiner found that Dong described a GLP-1 analogue identical to claim 15's GLP-1 analogue having SEQ ID NO: 767, except that Dong's GLP-1 analogue had a glycine at position 8, rather than serine (Ans. 3-4 (citing Dong 40:8 ("Example 378 (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂"))).

To address that difference, the Examiner cited Deacon as teaching that "substitutions at the 8th position with Gly or Ser of the GLP-1 molecule still are biologically active and have prolong[ed] metabolic stability in vivo" (*id.* at 4). The Examiner also noted Deacon's teaching that "the Ser8 analog was more stable than the Gly8" (*id.*).

The Examiner reasoned, therefore, that an ordinary artisan would have considered it obvious to substitute Serine for Glycine at position 8 of Dong's GLP-1 analogue "because Serine in position 8 provides for more stability

¹ WO 00/34331 A2 (published June 15, 2000).

² C. F. Deacon et al., *Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity*, 41 DIABETOLOGIA 271-278 (1998).

relative to Glycine at position 8. There would have been a reasonable expectation of success because Deacon et al. demonstrates that it takes longer for a Ser8-GLP-1 analog to be degraded by porcine plasma than wild type GLP-1 and Gly8-GLP-1” (*id.*).

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.

Appellant initially argues there is “nothing in the references of record to lead a person of ordinary skill in the art to select the compound (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂ out of a disclosure of 411 specific GLP-1 analogues in [Dong] for further modification” (App. Br. 7 (underlining omitted); *see also* Reply Br. 3-11).

In particular, Appellant argues, “[t]he courts have made it clear that there must be something in the prior art that leads a person of ordinary skill in the art to make such selection as a ‘lead compound,’ or a compound that would be most promising to modify, in formulating the claimed compound” (App. Br. 7). However, Appellant urges, “[n]o data are presented in [Dong], absent molecular weight and purity data, that would guide a person of ordinary skill in the art to make the selection” of (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂ as a lead compound that an ordinary artisan would have sought to improve (*id.* at 8).

We do not find Appellant’s argument persuasive.

“Obviousness based on structural similarity . . . can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.” *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008).

Thus, in evaluating the prima facie obviousness of a new chemical compound in view of similar prior art compounds, one must first determine “whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts.” *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012).

As Appellant notes, our reviewing court has further advised:

While the lead compound analysis must, in keeping with *KSR [Int’l v. Teleflex Inc.]*, 550 U.S. 398 (2007)], not rigidly focus on the selection of a single, best lead compound . . . , the analysis still requires the challenger to demonstrate . . . that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art.

Daiichi Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (citation omitted).

Here, as the Examiner pointed out, Dong discloses a compound that differs from the claimed compound only in that Dong’s compound has glycine at position 8, rather than the serine of elected compound (*see* Dong 40 (Example 378 (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂)). We acknowledge, as Appellant argues, that Example 378 is one of 411 exemplified compounds, and is a single species of a broader generic disclosure (*see* Dong *generally*).

Nonetheless, Dong discloses, as a general principle, that “the administration of *the compounds of this invention* for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself” (*id.* at 16 (emphasis added) (listing over 20 treatable disorders, including Type I and Type II diabetes)). Thus, we are not persuaded that Dong failed to provide a reason to select any of its exemplified compounds, including Example 378, as a compound suitable for further improvement.

It may true, as Appellant argues, that Dong provides no specific biological activity data for any of the exemplified GLP-1 analogues that might allow an ordinary artisan to choose one of Dong’s compounds over another as a lead compound. Appellant points to no evidence of record, however, suggesting that an ordinary artisan would have expected any of the exemplified compounds, including the compound of Example 378, to lack the therapeutic properties described in Dong. Moreover, Appellant points to no evidence of record suggesting that an ordinary artisan would have ignored Dong’s general teaching of therapeutic efficacy, and instead only would have selected as lead compounds those compounds for which specific comparative data had been presented.

We note the statement in *Daiichi Sankyo* that, while the inquiry should not rigidly focus on a single lead compound, “the analysis still requires the [claim] challenger to demonstrate . . . that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds *over other compounds in the prior art.*” *Daiichi Sankyo v. Matrix Labs.*, 619 F.3d at 1354 (emphasis added); *see also Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012) (“A lead compound, as we have explained, is ‘a compound in the prior art that would

be *most promising* to modify in order to improve upon its ... activity and obtain a compound with better activity.” (Emphasis added.) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

We are not persuaded, however, that *Daiichi Sankyo, Otsuka*, or other lead compound cases mandate that the only compounds useful for evaluating obviousness are those for which the prior art has provided specific comparative data. In this case, for example, accepting such an interpretation would effectively render Dong unavailable as prior art for determining obviousness, simply because Dong did not provide data comparing the biological properties of its compounds.

Such an outcome conflicts with the well settled broader principle that, when evaluating claims for obviousness, “the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill.” *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986); *see also Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (“[I]n a section 103 inquiry, ‘the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.’”) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)).

Moreover, as noted above, the Federal Circuit has tempered the rigorousness of the lead compound analysis by stating that “the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound” *Daiichi Sankyo v. Matrix Labs.*, 619 F.3d at 1354 (citing *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)).

In sum, given Dong's teaching that its compounds possess GLP-1-like therapeutic activity, we are not persuaded that the Examiner erred in finding that an ordinary artisan had a reason to select the compound of Dong's Example 378 for further improvement. As discussed below, we are also not persuaded that the Examiner erred in finding that Deacon would have prompted an ordinary artisan to substitute serine for the glycine at position 8 of Dong's compound.

Deacon, like Dong, discloses that GLP-1 "has great potential in diabetes therapy due to its glucose-dependent stimulation of insulin secretion, but this is limited by its rapid degradation, primarily by dipeptidyl peptidase IV [DPP IV]" (Deacon 271 (abstract); *see also* Dong 2 ("This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.")).

Deacon thus undertook a study to examine "whether small modifications of the N-terminus of GLP-1 would also confer resistance to degradation by DPP IV, while retaining the peptide's biological activity" (*id.* at 272). To perform the study, "[a]nalogues, substituted at position 8 of GLP-1 with either threonine (Thr⁸-GLP-1 (7-37)), glycine (Gly⁸-GLP-1 (7-37)), serine (Ser⁸-GLP-1 (7-36) amide) or α -aminoisobutyric acid (Aib⁸-GLP-1 (7-36) amide and Aib⁸-GLP-1 (7-37)) were prepared" (*id.*).

Testing for stability, Deacon found that the native "GLP-1 (7-36) amide was degraded by porcine plasma in vitro at 37°C; with a $t_{1/2}$ of 28.1 ± 1.2 min ($n = 12$)" whereas "[i]ncubation of the GLP-1 analogues revealed a significantly ($p < 0.0001$) prolonged $t_{1/2}$ compared to GLP-1 (7-36) amide itself (Gly⁸-GLP-1, 159 ± 12 min, $n = 3$; Ser⁸-GLP-1, 174 ± 12 min, $n = 9$;

Thr⁸-GLP-1, 197 ± 14 min, *n* = 3)” with “[d]egradation of Aib⁸-GLP-1 (*n* = 9) being undetectable after 6 h” (*id.* at 273). Given the serine-substituted analogue’s significant stability improvement over the native peptide, as well as its superiority over the glycine analogue, we agree with the Examiner that Deacon would have prompted an ordinary artisan to substitute serine for the glycine at position 8 of the compound described in Dong’s Example 378.

We note, as Appellant argues (*see* App. Br. 10), that the serine substitution at position 8 did not produce the most stable GLP-1 analogue (*see* Deacon 273). As Appellant points out, the serine substituted analogue also did not have the highest receptor binding affinity of the tested analogues (*id.* at 274 (“The Aib⁸ and Gly⁸ analogues had similar affinities compared to GLP-1 (7-36) amide, while the other two analogues had lower receptor affinities than GLP-1 (7-36) amide.”)). As Appellant further points out, while the serine substituted analogue exhibited biological activity when contacted with isolated pancreas, it was not the most potent of the analogues tested:

Of the analogues, Aib⁸-GLP-1 (7-36) amide was at least as potent as GLP-1 (7-36) amide in stimulating insulin and inhibiting glucagon secretion, and was significantly (*p* < 0.05) more potent than the Ser⁸ and Thr⁸ analogues in raising insulin output. It was also the most potent (*p* < 0.05) of all the analogues in reducing glucagon output. The Gly⁸ analogue was not significantly different to GLP-1 (7-36) amide in stimulating insulin or inhibiting glucagon secretion, but was more potent (*p* < 0.05) than the Ser⁸ and Thr⁸ analogues in inhibiting glucagon release, while the Thr⁸ analogue was the least potent of the analogues tested.

(*Id.* at 274-275.)

However, as the Examiner points out, “a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination.” *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). Moreover, the “prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed. . . .” *Id.* at 1201.

Here, both Dong and Deacon teach the desirability of modifying GLP-1 so as to improve its stability, and as the Examiner found, Deacon discloses that substituting a serine at position 8 of the native GLP-1 sequence results in a biologically active analogue which is significantly more stable than native GLP-1, and which is also more stable compared to an analogue having a glycine at position 8. While it might be true that an ordinary artisan may have considered the serine substitution to be less desirable than other substitutions tested by Deacon, that fact does not demonstrate that an ordinary artisan would have considered the serine substitution unobvious. *See In re Fulton*, 391 F.3d at 1200-1201.

Turning to the issue of unexpected results, “while not directly relating to the rejections on Appeal, Appellant notes that multiple Rule 132 Declarations have been submitted during the prosecution of the application to show the surprising and unexpected qualities of the elected species (Ser⁸,

Aib³⁵)hGLP-1(7-36)NH₂” (App. Br. 12 (citing Zhang Declaration³ and Taylor Declaration⁴)).

However, as the Examiner argues, neither of comparisons presented in the Declarations and reproduced in the Appeal Brief compares the compound under examination to the compound from Example 378 of Dong, (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂, which forms the basis of the Examiner’s obviousness rejection. Thus, as Appellant appears to concede (*see* App. Br. 12 (“while not directly relating to the rejections on Appeal”)), the comparisons Appellant advances to show unexpected results are not comparisons to the closest prior art. *Compare In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) (“[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.”).

Moreover, while Appellant argues that the results presented in the Zhang and Taylor Declarations are “surprising and unexpected” (App. Br. 12), Appellant points to no instance in either Declaration where the Declarant actually states that the results obtained were unexpected. Thus, the actual evidentiary showings Appellant relies on to show unexpectedness lack clear or specific factual support for such a finding. *Compare In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997) (argument by counsel cannot be substituted for actual evidence of unexpected results).

³ Declaration of Jundong Zhang, Ph.D. under 37 C.F.R. § 1.132 (declaration executed February 27, 2009).

⁴ Declaration of John E. Taylor, Ph.D. under 37 C.F.R. § 1.132 (declaration executed February 27, 2009).

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In sum, for the reasons discussed, Appellant's arguments do not persuade us that a preponderance of the evidence fails to support the Examiner's prima facie case of obviousness, nor are we persuaded that Appellant has advanced evidence of unexpected results sufficient to outweigh that prima facie case. Accordingly, we affirm the Examiner's rejection of claim 15 over Dong and Deacon.

Claims 16-18 fall with claim 15. *See* 37 C.F.R. § 41.37(c)(1)(vii).

SUMMARY

We affirm the Examiner's obviousness rejection of claims 15-18 over Dong and Deacon.

TIME PERIOD

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

AFFIRMED

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