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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/928,689	10/30/2015	JOHN P. SHEEHAN	WARF.P0050US	8987

108197 7590 09/16/2019

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
09/16/2019	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOHN P. SHEEHAN and PANSAKORN TANRATANA

Appeal 2019-004134
Application 14/928,689
Technology Center 1600

BEFORE RYAN H. FLAX, RACHEL H. TOWNSEND, and CYNTHIA M. HARDMAN, *Administrative Patent Judges.*

HARDMAN, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject certain claims directed to variants of Factor IX as obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as "Wisconsin Alumni Research Foundation." Appeal Br. 3.

STATEMENT OF THE CASE

According to the Specification, the invention concerns "variants of Factor IX which can be used in improved methods of treating hemophilia." Spec. 2:16–17. Claim 1, reproduced below, is illustrative of the claimed subject matter:

> 1. A Factor IX protein comprising a R→A substitution at residue 150 of the native human Factor IX sequence and either but not both (a) a K→A substitution at residue 126 of the native human Factor IX sequence or (b) a K→A substitution at residue 132 of the native human Factor IX sequence, as defined by the human chymotrypsinogen numbering system for the protease domain.

Appeal Br. 14 (Claims Appendix).

Claims 1–6, 8, 9, 26, and 28 are on appeal. Final Act. 2. The claims stand rejected under 35 U.S.C. § 103 as being unpatentable over Westmark II[2] and Westmark I.[3] *Id.* at 9–10.

ANALYSIS

The Examiner rejected the claims as being obvious over Westmark II and Westmark I. Final Act. 9–10. According to the Examiner, Westmark II discloses "human FIX proteins comprising alanine substitutions [] in the

[2] Westmark et al., *Selective mutagenesis of the heparin and antithrombin exosites on human factor IX(a) enhances thrombin generation in human plasma*, Presentation, ISTH Meeting Amsterdam, Netherlands, July 2013 ("Westmark II").
[3] Westmark et al., *Selective mutagenesis of the heparin and antithrombin exosites on human factor IX(a) enhances thrombin generation in human plasma*, Abstract, ISTH Meeting, Amsterdam, Netherlands, July 2013 ("Westmark I").

heparin binding exosite (K126A, K132A, K126A/K132A)[4], antithrombin-binding exosite (R150A), or both (K126A/K132A/R150A)." *Id.* at 10. The Examiner found that Westmark II further discloses "optimized combinations of exosite mutations, such as K126A/R150A or K132A/R150A" (*id.*), which are the two double mutations recited in the claims. The Examiner found that one of ordinary skill in the art would have arrived at the claimed proteins with the claimed mutations because Westmark II discloses that these double mutations "may yield proteins with prolonged in vivo half-life and enhanced activity." *Id.*

With respect to reasonable expectation of success, the Examiner stated:

> Westmark I disclose that in contrast to their clotting activities, both FIX R150A and K126A demonstrated markedly enhanced TF-initiated TG [tissue factor-initiated thrombin generation] relative to WT [wildtype] protein (≥ 2 fold) (results) and Westmark II disclose K126A, K132A, and R150A support substantial levels of TF-triggered thrombin generation (slide 14). . . .
>
> While the combined heparin exosite mutations FIX K126A/K132A have reduced thrombin generation proportionate to clotting activity (~20%), it is disclosed that addition of R150A (triple mutant) increased TG activity of the K126/K132A FIX zymogen and protease forms (Westmark I results; Westmark II slides 11, 13). Mutation of the antithrombin-binding site (R150A) tended to increase plasma TG relative to clotting activity, either alone or in the context of combined mutations in the heparin-binding exosite (double vs. triple mutant) (Westmark I conclusion).

[4] We understand this nomenclature to mean that, e.g., at position 126 of the protein's amino acid sequence the K is substituted with A, and at position 132 the K is substituted with A.

> Therefore, given that it was recognized that the antithrombin-binding site mutation (R150A) markedly enhanced TG relative to WT protein (≥ 2 fold) and tended to increase plasma TG relative to clotting activity, one of ordinary skill would have a reasonable expectation of success that the combination of an antithrombin and heparin exosite mutation (i.e. R150A/K126A and R150A/K132A) would yield FIX variants having significantly enhanced TG activity since FIX K126A, like R150A, was also demonstrated to have markedly enhanced TG relative to WT protein (≥ 2 fold) and FIX K132A had TG activity similar to WT FIX.

Ans. 6–7.

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (*id.* at 9–13; Ans. 3–11), and agree that claims 1–6, 8, 9, 26, and 28 would have been obvious over Westmark II and Westmark I for the reasons the Examiner articulated. Indeed, Westmark II expressly suggests two specific, "optimized" combinations of exosite mutations, K126A/R150A and K132A/R150A, which are the very same double mutations recited in Appellant's claims. We note, both Westmark I and Westmark II are prior art publications (it is not disputed), co-authored by one of the named inventors, on the subject matter of the appealed claims.

Appellant argues a lack of reasonable expectation of success, asserting that "the general expectation is that making mutations in molecules like those claimed here would lead to decreased activity." Appeal Br. 9. As support for this assertion, Appellant points to Tables 1 and 2 in the Specification, arguing that the "single substitution mutants K126A, K132A and R150A lost varying degrees of thrombin generation activity" as compared to wildtype, while double and triple substitution mutants (K126A/R150A, K132A/R150A, K126A/K132A/R150A) lost varying degrees of coagulant activity as compared to wildtype. *Id.* at 9–11.

Appellant argues that the "take away" from these data and from Westmark II is that "most mutations tend to ***reduce*** activity, not improve it," and that "***any*** given double mutant would be expected to ***lose*** activity of all types." *Id.* at 10; *see also id.* at 11 (arguing that "Westmark II shows that a double mutant lost activity, which would ***discourage***, not encourage the skilled artisan, and also would eliminate any reasonable expectation of success").

We are not persuaded by Appellant's argument that a person of ordinary skill in the art would have held a "general expectation" that all mutations in Factor IX proteins would lead to decreased activity. First, Appellant's reliance on data in the Specification is irrelevant. Obviousness and reasonable expectation of success are "measured from the perspective of a person of ordinary skill in the art *at the time the invention was made*." *Velander v. Garner*, 348 F.3d 1359, 1379 (Fed. Cir. 2003) (emphasis added). Accordingly, our focus must be on the information available in the prior art. Appellant has not established that the data in Table 2 of the Specification were known in the prior art, and in fact, Appellant has argued that the data in the Specification are more "complete" and "mature" than the data in Westmark I and II. *See* Reply Br. 4, 5 n.1.

Second, Appellant's argument overstates the purported "take away" from Westmark II. According to Westmark II, the double mutation K126A/K132A in the heparin binding exosite markedly reduced coagulant and thrombin generation activity. *See* Westmark II at slide 14. But, there is no basis to extrapolate this to a broader teaching that ***all*** double mutants would be expected to lose activity of ***all*** types. To the contrary, Westmark II teaches that "optimized combinations of exosite mutations," such as a double mutation comprised of one mutation in the heparin binding exosite

(either K126A or K132A) and one mutation in the antithrombin binding exosite (R150A), "may yield proteins with prolonged in vivo half-life and enhanced activity." *See id.*

In the Reply Brief, Appellant argues that we should discount the data in Westmark I and II because they are "preliminary," and because "discrepancy in the data sets of Westmark I and II was clearly evident." Reply Br. 4–7. Appellant argues that the "discrepancy" was found to be caused by protease contamination, which purportedly caused "substantial[] overestimat[ion]" of the amount of thrombin generation in the zymogen samples. Appellant thus asserts that "reliance on this clearly inconsistent and facially unreliable data is completely misplaced." *Id.* at 7.

We are not persuaded by Appellant's arguments. In the Appeal Brief, Appellant cites a "subsequent analysis" of protease contamination in the zymogen samples (*see* Appeal Brief 11, citing Westmark 2015[5]), but did not attempt to establish that the purported contamination would have been known to a person of ordinary skill in the art at the time of Appellant's invention. In the Reply Brief, Appellant argues for the first time that "the presence of contaminating FIXa in zymogen preparations has been previously recognized." Reply Br. 6. This argument was not timely presented, and is therefore waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex Parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that

[5] Westmark et al., *Selective disruption of heparin and antithrombin-mediated regulation of human factor IX*, 13 J. Thromb. Haemost. 1053–63 (2015) ("Westmark 2015").

are not raised in the principal brief [but could have been to rebut the Examiner's rejection] are waived.").

However, even if we were to assume that a person of ordinary skill in the art would have known at the time of Appellant's invention that protease contamination could affect zymogen samples in the thrombin-generation assay, the record nevertheless lacks evidence that a person of ordinary skill in the art would have wholly ignored the zymogen results presented in Westmark I and II because of potential contamination. In fact, Westmark 2015 states that only two zymogen samples, K132A and R150A, were contaminated, such that thrombin generation was "likely mildly or moderately overestimated" for samples K132A and R150A, respectively. Westmark 2015 at 1061. Westmark 2015 further states that three other zymogen samples were not contaminated, and that "the higher TG activity demonstrated by rFIX K126A, K126A/R150A, and K132A/R150A cannot be explained by protease contamination." *Id.* The Specification additionally states that contamination does not explain the higher TG activity demonstrated by the triple mutant (K126A/K132A/R150A) relative to coagulant activity. Spec. 68:7–9.

Accordingly, we are not persuaded by Appellant's argument that a person of ordinary skill in the art would have discounted data in Westmark I or II based on the purported "preliminary" nature of the data, purported inconsistencies, or purported contamination.

Appellant next asserts that statements on Westmark II slide 14 "should not be permitted to argue in favor of obviousness." Reply Br. 7. Specifically, Appellant argues that the reference to "substantial" levels of thrombin generation for K126A, K132A, and R150A on slide 14 "does not

infer that these levels are greater than" wildtype activity, because each of these mutants had "somewhat reduced" activity compared to wildtype. *Id.* at 6–8. These arguments are not persuasive, because they ignore the zymogen data in Westmark I, which indicated that the K126A and R150A zymogens "demonstrated markedly enhanced TF-initiated TG relative to WT protein (≥ 2-fold)," and that K132A had thrombin generation similar to that of wildtype. *See* Westmark I (Results). For the reasons discussed above, we decline to ignore this zymogen data. When read in the context of the zymogen data, the statement on Westmark II slide 14 is consistent with an inference that these mutants had at least the same or more thrombin generation than the wildtype protein.

Appellant also argues that the final point on Westmark II slide 14 is "forward-looking" and "speculative," because "***no experimental data existed to support it***." Reply Br. 7, 8. This is not persuasive, because for the reasons discussed above and by the Examiner, Westmark I and II contain sufficient data to support Westmark II's suggestion that the claimed double mutations "may yield proteins with prolonged in vivo half-life and enhanced activity." Final Act. 9–13; Ans. 3–11.

Appellant also argues that the claimed double mutants demonstrate surprising and unexpected properties. Appeal Br. 12. Relying on the data in Table 2 of the Specification, Appellant argues that "the fact that each of the three individual substitutions ***lost*** thrombin generation activity, as did K126A/K132A and the triple substitution, the ***increase*** in thrombin generation activity that appears ***only with K126A/R150A and K132A/R150A*** must be considered as highly unexpected." *Id.*

We are not persuaded by this argument, because it improperly discounts the zymogen data reported in Table 2 (and in the prior art). Focusing only on the right-hand columns of Table 2, Appellant is correct that only the claimed mutants showed an increase in thrombin generation activity compared to wildtype. Spec. 63 (Table 2). However, the zymogen data in the left-hand columns show that each of the K126A, K132A, and R150A single mutants showed increased thrombin generation activity compared to wildtype. *Id.* Even if we ignore the results for K132A and R150A due to contamination, K126A showed increased thrombin generation activity. Westmark 2015 at 1061; Spec. 68:5–7. The double mutant K126A/K132A showed reduced thrombin generation activity compared to wildtype, but this was explained in Westmark II, where the authors stated that these combined mutations, both of which are in the heparin binding exosite, "may synergistically reduce cofactor affinity." Westmark II (slide 14). Consistent with the teachings in Westmark I, Table 2 in the Specification indicates that addition of the R150A mutation to the K126A/K132A double mutant increased thrombin generation. Spec. 63 (Table 2). Thus, when viewing the entire collection of data (including the zymogen data in the left-hand columns of Table 2), we disagree with Appellant that the claimed double mutations (K126A/R150A and K132A/R150A) are the only mutations that resulted in increased thrombin generation.

CONCLUSION

We affirm the obviousness rejection of claims 1–6, 8, 9, 26, and 28 as being obvious over Westmark II and Westmark I.

In summary:

Claims Rejected	Basis	Affirmed	Reversed
1–6, 8, 9, 26, and 28	§ 103 Westmark II, Westmark I	1–6, 8, 9, 26, and 28	

TIME PERIOD FOR RESPONSE

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

AFFIRMED