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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MASAAKI TOYODA[1]

Appeal 2020-002135
Application 15/758,593
Technology Center 1600

Before ERIC B. GRIMES, FRANCISCO C. PRATS, and ULRIKE W. JENKS, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for preparing an antibody sugar chain, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

STATEMENT OF THE CASE

"[T]he present invention relates to a method of rapidly preparing a sugar chain from a glycoprotein." Spec. ¶ 1. "Specific examples of the

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[1] Appellant identifies the real party in interest as Sumitomo Bakelite Co. Ltd. Appeal Br. 2. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

glycoprotein include . . . an antibody." Spec. ¶ 16. "In a case where a glycoprotein [is] an antibody, it is particularly important to analyze a sugar chain. In this case, it is possible to rapidly isolate a sugar chain that influences the activity or the like of the antibody." Spec. ¶ 17.

In an embodiment, "a sugar chain can be extremely rapidly prepared from a glycoprotein in the form (labeled form) of a sample for analysis by isolating a sugar chain on a solid phase without eluting a glycoprotein fixed to the solid phase, and adding a labeling reagent (labeling reaction solution) to the container without separating the isolated product." Spec. ¶ 11. "[I]t is preferable to purify the sugar chain from the mixed solution before the analysis in a case where the analysis is carried out by means of mass analysis or the like." Spec. ¶ 79. "By means of the analysis of the glycoprotein sugar chain as described . . . it becomes possible to accelerate research and development of antibody pharmaceutical products." Spec. ¶ 130.

Claims 23–30 are on appeal.[2] Claim 23, reproduced below, is illustrative:

> Claim 23: A method for preparing a glycoprotein sugar chain, comprising:
>
> an isolation step of acting a sugar chain-isolating enzyme on a sample which contains a glycoprotein fixed to a solid phase in a container to obtain an isolated product which contains a sugar chain; and

[2] The Examiner included claim 39 in the rejection but this claim was canceled in the amendment filed May 20, 2019. The amendment was entered by the Examiner. *See* Advisory Action mailed June 7, 2019.

> a labeling step of adding a labeling reagent to the isolated product without purifying the sugar chain from the isolated product to obtain a labeled product which contains a labeled substance of the sugar chain, wherein
>
> the glycoprotein is an antibody, and the solid phase includes a ligand selected from the group consisting of protein A, protein G, protein L, protein H, protein D, and protein Arp, in the surface thereof, and
>
> the amount the glycoprotein is in a range of 0.001 to 500 μg per one container.

The claims stand rejected as follows:

Claims 23–25 and 27–30 under 35 U.S.C. § 103 as being unpatentable over Tayi[3] and Ruhaak (2008)[4] (Ans.[5] 3);

Claims 23–30 under 35 U.S.C. § 103 as being unpatentable over Tayi, Ruhaak (2008), and Ruhaak (2011)[6] (Ans. 7).

OPINION

Obviousness based on Tayi and Ruhaak (2008)

Claims 23–25 and 27–30 stand rejected under 35 U.S.C. § 103 as being obvious over Tayi and Ruhaak (2008). Final Action 4. The Examiner finds that Tayi "teaches a method wherein a sugar chain isolating enzyme (PNGase F) acts on a sample containing a glycoprotein (antibody) fixed to a

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[3] Tayi et al., "Isolation and quantification of N-glycans from immunoglobulin G antibodies for quantitative glycosylation analysis," Journal of Biological Methods 2(2):1–8 (2015).
[4] Ruhaak et al., "Hydrophilic Interaction Chromatography-Based High-Throughput Sample Preparation Method for N-Glycan Analysis from Total Human Plasma Glycoproteins," Anal. Chem. 80:6119–6126 (2008).
[5] Examiner's Answer mailed Nov. 22, 2019.
[6] Ruhaak, WO 2011/038873 A1, published April 7, 2011.

solid phase (bead) including a ligand (protein-A or protein-G) . . . to obtain an isolated product which contains a sugar chain (N-glycans)." Final Action 4. The Examiner finds that Tayi also teaches "adding a labeling reagent . . . to the isolated product in a container to obtain a labeled product which contains a labeled . . . sugar chain." *Id.*

The Examiner finds that Tayi "does not teach a method wherein the labeling step is performed without purifying the sugar chain from the isolated product." Final Action 5.[7] The Examiner finds that Ruhaak (2008) "teaches a high throughput method for preparing a glycoprotein sugar chain" that, like Tayi's method, treats "a glycoprotein (citrate plasma)" with PNGase F "to obtain an isolated product which contains a sugar chain (N-glycans)." *Id.* The Examiner also finds that Ruhaak (2008) teaches adding a labeling reagent "to the isolated product without purifying the N-glycans from the isolated product to obtain a labeled sugar chain." *Id.* The Examiner finds that Ruhaak (2008) "teaches that prior art methods require purification systems not available to every laboratory or are labor intensive and time-consuming." *Id.*

The Examiner concludes that it would have been obvious to one of ordinary skill in the art "to modify the method of preparing labeled N-glycans from antibodies which requires a purification step prior to labeling" as taught by Tayi with the method of Ruhaak (2008) "for preparing labeled N-glycans which does not require a purification step prior to labeling as this

[7] The Examiner also states that Tayi does not teach 0.001 to 500 μg of glycoprotein per container. Final Action 5. However, the Examiner later corrected himself, and noted that "Tayi *et al.* discloses the addition of 50–100 μg of antibody (glycoprotein) into a container." Ans. 11.

would decrease the preparation time of the method of Tayi *et al*. by eliminating a method step, resulting in time and labor savings." Final Action 6.

Appellant argues that "there is no correlation between the process of Ruhaak (i.e. isolating glycoproteins from citrate plasma which were denatured, subsequently releasing N-glycans using PNGase, and thereafter labeling the released N-glycans) and the results obtained thereby with the distinctly different process of the primary reference Tayi." Appeal Br. 7. Appellant argues that "the process of Tayi requires that the sugar chain is purified from an isolated product . . . and a labeling step is performed by adding a labeling reagent to the purified sugar chain." *Id.* Appellant concludes that "[t]he skilled artisan would not find an expectation of success [in] removing these steps from Tayi based on the Ruhaak process." *Id.*

Appellant states that "the glycoprotein of the present invention has been limited to an antibody, and the antibody is fixed to a solid phase via a ligand" that has an affinity for the antibody. Appeal Br. 8. Appellant argues that "Ruhaak does not provide for limiting a glycoprotein to an antibody, and does not provide for fixing an antibody to a solid phase via a ligand having an affinity for the antibody." Appeal Br. 8–9. Appellant concludes that "the skilled artisan has no manner of deriving to simply remove the purification step taught by Tayi as an obvious modification based on Ruhaak when the processes of each are completely different in their approach to isolating and labeling." Appeal Br. 9.

We agree with the Examiner that the claimed method would have been obvious to a person of ordinary skill in the art based on Tayi and

Ruhaak (2008). Tayi discloses a "method of isolating N-glycans from Immunoglobulin G based antibodies for glycosylation analysis" consisting of "purification of antibodies from biological solution and release of N-glycans with peptide-N-glycosidase F in a single consolidated process using a mini affinity ligand column." Tayi, Abstract. "The isolated glycans can be labeled with 2-aminobenzamide (2-AB) or 2-Aminobenzoic acid (2-AA)." *Id.* at 4.

Ruhaak (2008) similarly discloses a procedure wherein "N-glycans are released from glycoproteins and subsequently labeled with 2-AA without prior purification." Ruhaak (2008), Abstract. Ruhaak (2008) states that its method is a "high-throughput procedure for rapid preparation of 2-aminobenzoic acid (2-AA) labeled N-glycans from . . . human plasma." *Id.*

Thus Tayi, like Ruhaak (2008), enzymatically releases N-glycans from a protein. The Examiner relies upon Ruhaak (2008) only to show that the isolated N-glycans are effectively labeled without purifying them after they are released from glycoproteins. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). Here, a skilled artisan would have considered it obvious to modify Tayi's method by labeling cleaved glycans without purifying them, because Ruhaak (2008) teaches that pre-labeling purification is unnecessary.

Appellant states that in Tayi, "after an isolation step is performing [sic] . . . a sugar chain is purified from an isolated product (see Tayi, page 3, PROCEDURE 2, item 2.7 'Filter the glycans through 10K filter and collect

the filtrate into 1.5 ml micro-centrifuge tube', etc.), and a labeling step is performed by adding a labeling reagent to the purified sugar chain." Appeal Br. 5. Appellant has not, however, provided any evidence to indicate that eliminating the filtration step of Tayi (as suggested by Ruhaak (2008)) would prevent effective labeling of the N-glycans.

Appellant argues that the method of claim 23 "has unexpected remarkable effects and therefore demonstrates criticality pursuant to M.P.E.P §2144.05.III." Appeal Br. 4. Appellant states,

> [f]or example, when a sugar chain isolation and a sugar labeling were performed on Protein A-binding monolith silica (see, Example 2), the time taken for all steps was approximately 3 hours. On the other hand, when a sugar chain isolation using a deglycosylation promoter and a sugar chain labeling were performed after a sugar chain purification were performed on Protein A-binding monolith silica (see, Reference Example 1), the time taken for all steps was 7 hours.

Id.

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). In this case, Tayi's sugar chain purification method differs from the sugar chain purification method disclosed in Reference Example 1 of the Specification. As noted by Appellant, in Tayi's method, a sugar chain is purified by filtering the glycans through a filter and collecting the filtrate, after which a labeling step is performed. Appeal Br. 5.

By contrast, in the sugar chain purification method disclosed by Reference Example 1, "[t]he isolated sugar chain was captured by bringing the separate liquid into contact with sugar chain purification kit BlotGlyco

(registered trademark) beads (manufactured by Sumitomo Bakelite Co., Ltd.), and then re-isolation (purification of the isolated sugar chain) of the captured sugar chain and labeling with 2-aminobenzamide (2AB) were performed." Spec. ¶ 180. The isolated sugar chain purification step by filtration disclosed by Tayi is distinct from the isolated sugar chain purification step by capture upon purification beads followed by re-isolation disclosed by Reference Example 1. Thus, Appellant's comparison of Example 2 with Reference Example 1 is not sufficient to demonstrate that the claimed method is unexpectedly superior when compared with the closest prior art (Tayi).

In any event, Appellant has not persuasively explained why eliminating the sugar chain purification step described in Reference Example 1 would not be expected to result in a shorter processing time as described in Example 2. As the Examiner pointed out, modifying Tayi's method as suggested by Ruhaak (2008) "would decrease the preparation time of the method of Tayi *et al.* by eliminating a method step, resulting in time and labor savings." Final Action 6.

With respect to the amount of glycoprotein per container recited in claim 23, Appellant argues that "the amount is critical in that isolating and labeling such a small amount is extremely useful when limited sample size is available. . . . [T]he Examiner has not identified in the primary reference Tayi, or any other prior art, a process which isolates and labels a sample size within this claimed range." Appeal Br. 9–10.

This argument is unpersuasive. As noted above, Examiner found that "[w]ith regard to the amount of glycoprotein in a range of 0.001-500 μg per

one container" Tayi discloses "the addition of 50-100 µg of antibody (glycoprotein) into a container (column) (see Pg. 3, Procedure, Line 8)." Ans. 11.

We conclude that the rejection of claims 23–25 and 27–30 under 35 U.S.C. § 103(a) based on Tayi and Ruhaak (2008) is supported by a preponderance of the evidence, and we therefore affirm it.

Obviousness based on Tayi, Ruhaak (2008), and Ruhaak (2011)

Claims 23–30 stand rejected under 35 U.S.C. § 103 as being obvious over Tayi, Ruhaak (2008), and Ruhaak (2011). Final Action 7.

The Examiner finds that Tayi and Ruhaak (2008) are silent with respect to "a method wherein the reducing agent is picoline borane," but Ruhaak (2011) teaches that the sodium cyanoborohydride used by Ruhaak (2008) "may be too strong a reducing agent" and "2-picoline borane/2-PB is particularly effective for reductive amination of carbohydrate." Final Action 8. The Examiner concludes that it would have been obvious to modify the method of Tayi and Ruhaak (2008) "for preparing a labeled glycoprotein sugar chain comprising the use of the reducing agent sodium cyanoboro-hydride to use the 2-PB reducing agent as taught by Ruhaak [(2011)] because the reference teaches that they are art-recognized equivalent reducing agents." *Id.* We agree with the Examiner's fact-finding and conclusion.

Appellant argues that Ruhaak (2011) "does not provide for and is not relied upon in regard to the isolating and labeling steps of claim 23." Appeal Br. 10. We find this argument unpersuasive for the reasons discussed above.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
23–25, 27–30	103	Tayi, Ruhaak (2008)	23–25, 27–30	
23–30	103	Tayi, Ruhaak (2008), Ruhaak (2011)	23–30	
Overall Outcome			23–30	

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