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Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte GHOLAM A. PEYMAN

Appeal No. 2002-0784¹
Application No. 09/265,532

ON BRIEF

Before WILLIAM F. SMITH, SCHEINER and GRIMES, Administrative Patent Judges.
SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 3-15 and 24-26. Claim 27, the only other claim pending in the application, has been allowed.

Claims 1, 11, 15 and 24 are representative of the subject matter on appeal:

1. A process for inducing substantially complete posterior vitreous detachment of the vitreous from the inner limiting membrane of an eye, comprising the steps of

introducing a composition of a non-toxic amount of plasminogen and a non-toxic amount of a plasminogen activator into the vitreous of an eye of an animal, said composition of plasminogen and plasminogen activator being introduced in an effective amount to induce posterior vitreous detachment and said plasminogen activator being present in an amount to stimulate the conversion of plasminogen to plasmin, and contacting said composition with the vitreous for sufficient time to induce substantially complete posterior vitreous detachment without intraocular inflammation.

11. A process for inducing substantially complete posterior vitreous detachment of the vitreous from the retina in the eye of an animal, said process comprising the step

¹ As a preliminary matter, we note that this appeal is related to an appeal in application serial no. 09/475,474 (Appeal No. 2003-0562). We have considered the two appeals together.

of

injecting a composition into the vitreous of said eye in an amount to induce substantially complete posterior vitreous detachment in said eye without intraocular inflammation, said composition comprising a non-toxic amount of plasminogen, a non-toxic amount of urokinase and a pharmaceutically acceptable carrier.

15. The process of claim 11, wherein said composition further includes at least one selected from the group consisting of a chondroitinase, α -thrombin, dispase and transglutaminase.

24. A process for inducing substantially complete posterior vitreous detachment of the vitreous from the retina in the eye of an animal, said process comprising the step of

injecting a non-toxic composition into the vitreous of said eye in an effective amount to induce substantially complete posterior vitreous detachment in said eye without intraocular inflammation, said composition comprising about 0.01 units to about 16.0 units plasminogen, about 500 units to about 2500 units urokinase and a pharmaceutically acceptable carrier.

The references relied on by the examiner are:

Hageman	5,292,509	Mar. 8, 1994
Trese et al. (Trese)	5,304,118	Apr. 19, 1994
Kaplan et al. (Kaplan)	5,722,428	Mar. 3, 1998

Guyton, Textbook of Medical Physiology, 6th Ed., W.B. Sanders, pp. 98-99.

Hesse et al. (Hesse), "Tissue Plasminogen activator as a biochemical adjuvant in vitrectomy for proliferative diabetic vitreoretinopathy," Chemical Abstracts, Vol. 124, No. 13, abstract no. 16472w (1996)²

Claims 1, 3-15 and 24-26 stand rejected under 35 U.S.C. § 103 (a) as unpatentable over Trese, Guyton and Hesse, and as unpatentable over Trese, Guyton,

² This reference was erroneously referred to as "Lutz" throughout the prosecution of this application. Moreover, we note that neither the examiner nor appellant has provided the full text of this reference (Hesse et al. (Hesse), "Tissue Plasminogen activator as a biochemical adjuvant in vitrectomy for proliferative diabetic vitreoretinopathy," German J. Ophthalmol., Vol. 4, pp. 323-327 (1995)). Citation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document are prior art. See Ex parte Jones, 62 USPQ2d 1206, 1208 (Bd Pat. App. & Inter. 2001) (unpublished); MPEP 706.02 and April 29, 2002 internal policy Memo of Kunin. In this case, however, we consider the omission to be harmless, as the underlying reference was cited and relied on in related application serial no. 09/474,474 (Appeal No. 2003-0562). Finding no prejudice to appellant, we will consider the rejection on the merits as it comes to us.

Hesse, Hageman and Kaplan.

We affirm both of these rejections.

BACKGROUND

The vitreous is a clear, proteinaceous material which fills the posterior of the eye between the lens and the retina. The vitreous is attached at its posterior face to the retina at the vitreoretinal junction along the inner limiting membrane. The vitreoretinal junction is a layer of basement membrane proximal to the vitreous.

The inner limiting membrane of the retina contains type I and type II collagen, laminin, fibronectin and glycoconjugates. These components have been found to bind collagen fibers between the vitreous and the inner limiting membrane.

Vitreous traction is recognized as a serious and potentially blinding complication in a number of vitreoretinal diseases . . . An important aspect of most vitreoretinal surgery is to relieve the vitreous traction.^[3] Improvements have been made in mechanical vitrectomy techniques and instrumentation. However, the complete removal of the cortical vitreous from the retinal surface continues to be a difficult task.

Specification, page 2.

The process of the invention introduces a composition into the vitreous of the eye to induce complete posterior vitreous detachment . . . The composition includes plasminogen and a plasminogen activator for converting the plasminogen to plasmin . . . the plasminogen and activator have been found to produce cleavage at the vitreoretinal interface between the posterior vitreous cortex and the inner limiting membrane.

Specification, page 8.

Plasmin is unstable and must be utilized rapidly . . . In embodiments of the invention, the plasminogen is combined with a plasminogen activator enzyme in a suitable ophthalmic carrier prior to injecting into the vitreous of the eye. The composition containing both the plasminogen and the plasminogen activator will produce plasmin in situ or just prior to injecting so that it is desirable to introduce the composition into the vitreous of the

³ Vitreous traction refers to “[c]ontraction of opposing membranes acting to distort or detach underlying retinal tissue from its normal anatomical position and function.” From the “Glossary of Retinal Anatomy & Macular Pathology Terms,” available at <http://www.maculasurgery.com/Glossary.htm>, accessed July 3, 2003.

eye immediately after mixing to minimize conversion of the plasmin to the inactive form. Plasmin is produced in situ in the eye by the reaction between the plasminogen and the activator composition, as well as the reaction between the tissue plasminogen and the activator. In further embodiments of the invention, the plasminogen and the plasminogen activator are delivered to the vitreous of the eye simultaneously or sequentially through separate delivery devices . . . [or they] can be supplied to a common delivery device so that they mix as they are being introduced . . .

Specification, pages 13-14.

DISCUSSION

The examiner has rejected claims 1, 3-15 and 24-26 as obvious over the combined teachings of Trese, Guyton and Hesse, and also over the combined teachings of Trese, Guyton, Hesse, Hageman and Kaplan. As the examiner's proposed combination of Trese, Guyton and Hesse is central to both rejections, we will discuss the two rejections together.

Trese, Hesse and Guyton

Trese explains that "the vitreous is conventionally mechanically removed from the eye" during vitrectomy, and "simultaneously replac[ed] with a saline solution to prevent collapse of the eye." "One difficulty in performing a vitrectomy is that the vitreous exhibits a relatively strong adhesion to the retina of the eye," and "[m]echanical removal of the vitreous can result in scarring, tearing and other damage to the retina." Trese, column 1, lines 12-27. Trese describes an enzymatic method of inducing posterior vitreous detachment from the retina prior to vitrectomy, which "overcomes the above mentioned disadvantages" of mechanical removal of the vitreous. Id., line 35. "[P]lasmin is first introduced into the vitreous by any conventional means . . . after a relatively short period, for example five to sixty minutes following the introduction of the plasmin into the vitreous, the plasmin induces a posterior vitreous detachment, i.e., detachment of the vitreous from the retina." "Following posterior vitreous detachment,

the vitreous is removed from the eye by conventional means . . . due to the separation between the vitreous and the retina, the risk of damage from the vitreous removing means to the retina is minimized since scraping or other contact between the vitreous removing means and retina is either minimized or altogether eliminated.” Id., column 2, lines 5-21.

According to Hesse, plasminogen is present in the vitreous compartment of patients with proliferative diabetic vitreous retinopathy (PDVR); “tissue plasminogen activator (TPA) converts plasminogen to plasmin;” and “plasmin dissolves extracellular matrix protein in the vitreous interface.” “For that reason,” Hesse “used TPA in pars planar vitrectomy (ppV) of proliferative diabetic vitreous retinopathy (PDVR).” “Disintegration of the vitreous interface causes a posterior detachment of the vitreous body,” and vitrectomies “proved to be less difficult when TPA had been injected” 15 minutes before surgery; “[m]oreover, no severe bleeding occurred . . . in spite of marked PDVR.” As Hesse points out, plasminogen is not normally present at the vitreous-retina interface, but “[a]s the blood-retina barrier of diabetic patients has broken down, [it] can enter the vitreous compartment in these cases.” Abstract.

Guyton teaches that urokinase and streptokinase are plasminogen activators, that is, like TPA, they convert plasminogen to plasmin, “the agent disclosed by Trese as being useful for posterior vitreous detachment.” Answer, page 4.

The examiner bears the initial burden of establishing prima facie obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). “The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art.” In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991).

While it is true, as appellant argues, that “none of the cited references discloses the process of introducing plasminogen into the eye either alone or in combination with a plasminogen activator” (Brief, page 6), we agree with the examiner that the teachings of Trese, Hesse and Guyton, taken together, fairly suggest “substitut[ion of] the claimed combination of plasminogen and plasminogen activator [e.g, TPA or urokinase,] for the plasmin of Trese,” and moreover, that one skilled in the art “would have reasonably expected . . . that a combination of plasminogen and plasminogen activator would generate plasmin and would therefore function at least equivalently to the plasmin of Trese” in inducing posterior vitreous detachment. Answer, page 4. Where the prior art recognizes two components to be equivalent, an express suggestion to substitute one for another need not be present in order to render such substitution obvious. In re Fout, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982). Trese teaches that plasmin induces posterior vitreous detachment, while Hesse teaches that plasminogen, in combination with TPA, produces the same result. That is, when plasminogen is present in the vitreous, it is activated (converted to plasmin) in situ upon injection of TPA, and the plasmin “dissolves extracellular matrix protein in the vitreous interface,” and this “[d]isintegration of the vitreous interface causes a posterior detachment of the vitreous body, [] facilitating [vitrectomy].” Hesse, Abstract.

That being the case, we are not persuaded by appellant’s assertion that “Guyton has no relation to inducing posterior vitreous detachment,” and “does not suggest that a composition of plasminogen and a plasminogen activator is the equivalent of [] plasmin” (Brief, page 9), or appellant’s assertion that Hesse “discloses that tissue plasminogen activator can be used to dissolve blood clots and in pars planar vitrectomy,” but “does not suggest that plasmin can be produced in situ or that a

combination of plasminogen and a plasminogen activator can be or should be used to induce posterior vitreous detachment” (*id.*). Again, Hesse attributes the “disintegration of the vitreous interface [which] causes a posterior detachment of the vitreous body” (Abstract) to plasmin, generated by the action of TPA on plasminogen. In our view, one skilled in the art would have recognized that the effect of TPA and plasminogen on the vitreous interface would have been the same as the effect of plasmin.

Appellant acknowledges that Hesse “recognizes that tissue plasminogen activator converts plasminogen to plasmin,” but argues that Hesse “clearly fails to disclose a source of the plasminogen and clearly fails to suggest introducing plasminogen and tissue plasminogen activator into the eye” (Brief, page 10). However, it is clear that Hesse did not attribute the observed posterior vitreous detachment to TPA alone, but to the combination of TPA and endogenous plasminogen. Contrary to appellant’s argument that Hesse’s disclosure of TPA alone would have suggested “that the addition of plasminogen is unnecessary,” (*id.*, page 11), one skilled in the art would have recognized that plasminogen was necessary for detachment, but there was no need to inject it because it was already present in the vitreous of Hesse’s patients as the blood-retina barrier had been compromised by PDVR.

Appellant also argues that “the specification demonstrates that urokinase and plasminogen when used alone do not induce complete posterior vitreous detachment . . . [h]owever, the combination of urokinase and plasminogen when introduced together [is] effective in inducing substantially complete posterior vitreous detachment.” While the specification demonstrates that this is indeed the case, the argument does nothing to advance appellant’s position. Hesse teaches that plasminogen and TPA together induce posterior vitreous detachment, inasmuch as TPA converts plasminogen to

plasmin; similarly, Trese teaches that plasmin induces posterior vitreous detachment.

In any case, appellant argues that injecting a composition comprising plasminogen and a plasminogen activator into the vitreous is not equivalent to injecting plasmin alone, because the combination induces “substantially complete posterior detachment,” in which “the vitreous falls easily from the eye without any evidence of attachment” (Brief, page 7), but Trese “requires physical removal of the vitreous from the ocular cavity to completely separate the vitreous from the retina” (*id.*, page 8). Even though Trese discloses “that the scraping or contact of the retina is reduced or minimized or eliminated” when plasmin alone is injected, appellant argues that “this is not a specific disclosure that the vitreous detachment is complete . . . it only suggests that the detachment was sufficient for the suction device to remove the vitreous without mechanical scraping of the retina” (*id.*). Appellant also argues that this “does not contradict” another study, referred to at page 4, lines 5-24, of the present specification, that found that “plasmin alone . . . [is] ineffective in inducing complete posterior vitreous detachment” (page 8).

We have no reason to doubt that the present method induces substantially complete posterior detachment, however, having carefully reviewed the record, we cannot agree that it supports appellant’s assertion that Trese’s method does not produce the same result. First of all, appellant appears to be blurring the distinction between separation (i.e., detachment) of the vitreous from the retina, and removal of the vitreous from the ocular cavity. As explained in Trese, “vitrectomy involves the removal of the vitreous humor from the eye and the replacement of the vitreous humor by a sterile saline solution (column 1, lines 15-17), but “[o]ne difficulty in performing a

vitrectomy is that the vitreous exhibits a relatively strong adhesion to the retina of the eye” and “mechanical removal of the vitreous from the retina of the eye can result in scarring, tearing and other damage to the retina” (column 1, lines 24-27). Plasmin, on the other hand, “induces posterior detachment from the retina so that removal of the vitreous from the eye can be accomplished with only minimal risk of retinal damage during the vitrectomy” (column 1, lines 41-45). Similarly, the present specification indicates that, once “the desired extent of posterior vitreous detachment” has been achieved using a combination of plasminogen and a plasminogen activator, “[s]tandard vitrectomy surgical techniques are typically used to remove the vitreous from the eye and replace [it] with an ophthalmologically acceptable solution to stabilize the ocular cavity” (Specification, page 9), and also that the composition is “introduced into the vitreous . . . prior to or in combination with intraocular surgery to induce posterior vitreous detachment” (*id.*, page 15). Thus, the fact that Trese physically removes (i.e., suction) the vitreous from the ocular cavity during the vitrectomy has absolutely nothing to do with whether the vitreous was detached from the retina in preparation for its removal. In addition, we note that the only example in the present specification where the vitreous was allowed to “fall[] easily from the eye” to demonstrate complete detachment was one in which the eyes were dissected,⁴ hardly a procedure that could

⁴ “[R]abbits were sacrificed . . . Eyes were fixed . . . hemidissection of the globe was performed at roughly the horizontal meridian . . . dividing the globe into superior and inferior pieces which were inspected to ensure that the vitreous had been cut completely. Each piece of the globe was tilted, anterior segment down, and the vitreoretinal attachment was evaluated . . . If a total posterior vitreous detachment had occurred, the vitreous fell away from the retinal surface by gravity. If there was no posterior vitreous detachment or only partial separation, the vitreous was suspended from the eye cup.” Specification, page 20.

be performed on living patients. Specification, page 20.

Moreover, there is nothing in the plain language of Trese that would indicate that detachment is incomplete, especially as Trese states that “the risk of damage . . . to the retina is minimized since scraping or other contact between the vitreous removing means and retina is either minimized or altogether eliminated,” “due to the separation between the vitreous and the retina.” Finally, the other study referred to at page 4, lines 5-24, of the present specification, which purportedly found that plasmin alone did not induce complete posterior vitreous detachment, was one in which plasmin was injected “immediately prior to vitrectomy.” Trese, on the other hand, teaches that plasmin induces posterior vitreous detachment “five to sixty minutes following the introduction of the plasmin into the vitreous” (column 2, lines 9-10).

Finally, appellant argues that the amounts of plasminogen and urokinase required by certain of the claims “are not obvious matters of choice” because “the upper limit of the urokinase recited in claim 24 is [about 2500 units,]” but the specification shows that “5000 units of urokinase did not produce any measurable posterior vitreous detachment[,]” thus, “one skilled in the art would not be motivated to use less of an ineffective amount.” Brief, page 13. This argument is without merit. The fact that urokinase alone (at 1,000, 5,000 or 10,000 units) did not induce posterior vitreous detachment is of no moment; it is clear from the prior art that plasmin, or plasminogen activator combined with plasminogen to produce plasmin, induces posterior vitreous detachment. Moreover, Hesse was able to identify 25 µg of TPA (the same dose of TPA suggested at page 10 the present specification) as a safe and effective dose for inducing detachment, even when working with an unspecified amount of endogenous plasminogen, thus we agree with the examiner that “the determination of suitable amounts and carriers of plasminogen and plasminogen activator would have been a

routine matter of optimization of [] result effective parameters” (Answer, page 5).

“[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) (citations omitted).

Hageman and Kaplan

Claim 15 specifies that the composition “further includes at least one [of] . . . chondroitinase, α -thrombin, dispase and transglutaminase.” Hageman and Kaplan are relied on as evidence that chondroitinase and dispase, respectively, “are known to be useful in processes of vitreous detachment.” Appellant argues essentially that these two references “do not [remedy] the deficiencies of [Trese, Hesse and Guyton] so the combination of the five references do[es] not render the claimed process obvious.” Brief, page 13.

Nevertheless, for the reasons discussed above, we view the teachings of Trese, Hesse and Guyton as sufficient to suggest substitution of plasminogen and urokinase for plasmin in inducing posterior vitreous detachment. Inasmuch as Hageman and Kaplan teach that chondroitinase and dispase are useful in inducing vitreous detachment, we agree with the examiner that it would have been obvious for one skilled in the art “to have combined chondroitinase and/or dispase with the plasmin-generating combination of plaminogen/plasminogen activator, in order to take advantage of the vitreous-detaching properties [of] chondroitinase and dispase as well.” Answer, p. 11.

CONCLUSION

In our view, the references relied on by the examiner support a prima facie case

of obviousness, which Appellant has not rebutted. We therefore affirm the examiner's rejections of the claims under 35 U.S.C. § 103.

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

AFFIRMED

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William F. Smith)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
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Toni R. Scheiner)	APPEALS AND
Administrative Patent Judge)	
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