The opinion in support of the decision being entered today was not written
for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ALBERT T. NAITO

Appeal No. 2005-0126
Application No. 09/967,791

ON BRIEF

Before WILLIAM F. SMITH, ELLIS, and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-10 and 12-28, which are all of the claims pending in this application.

Claim 1 is illustrative of the claims on appeal and reads as follows:

1. A method for increasing the effect of a chemical compound within the body of a patient comprising administering said chemical compound to said patient, co-administering with said chemical compound a hypertonic sugar composition by a route other than by enteral administration or intravascular injection, and permitting said sugar composition to increase said effect, wherein said increase in effect of said chemical compound by said hypertonic sugar composition is by increasing the passage of said compound through the patient’s blood-brain barrier.

The prior art references cited by the examiner are:

Keep et al (Keep)	5,972,924	Oct. 26, 1999
Naito	EP 0652012 A1	May 10, 1995

Grounds of Rejection

Claims 1-10 and 12-28 stand rejected under 35 U.S.C. §103(a), as obvious in view of Naito and Keep.

We reverse this rejection.

DISCUSSION

Background

According to the background section of the specification describing the state of the art, the "blood-brain barrier that exists in all vertebrate brains was discovered in the latter part of the 19th century and the first half of the 20th century. Researchers discovered that dyes injected intravenously into the bloodstream stained all internal organs except the brain and that dyes injected into the cerebrospinal fluid stained cells of the brain but did not enter the bloodstream to stain other internal organs. It was later discovered that the blood-brain barrier was due to the structure of the capillary walls of the brain." Specification, page 1. "In organs other than the brain, fluid leaks out of the capillaries and enters the tissue through pores formed at the junction of adjacent endothelial cells. In the brain, however, endothelial cells of capillaries are intimately fused by intracellular tight junctions. The tight junctions prevent the paracellular

leakage of fluid from the capillaries, leaving transcellular flow from the capillary to the brain as the only means for fluid and solutes to enter the brain from the bloodstream." Id.

"Among the means of transcellular fluid flow available to other organs of the body, pinocytosis is virtually non-existent in brain capillaries. Consequently, solutes may enter the brain in one of two ways. Facilitated transport, a specialized carrier or receptor catalyst molecule transports a particular molecule through the endothelial cell wall into the brain. In lipid-mediated transport, small lipid molecules dissolve in and diffuse through the endothelial cell membrane. " Specification, pages 1-2.

"While these mechanisms permit entry into the brain of essential nutrients, the existence of the blood-brain barrier effectively prevents other substances, such as hormones, proteins, certain ions, and drugs from entering the brain." Specification, page 2.

According to the specification, it has been discovered that a hypertonic sugar composition is effective to promote the entry of a chemical substance, such as a nutrient or diagnostic or therapeutic agent, across the blood-brain barrier when the composition is administered to an animal by other than by gastrointestinal absorption or intravascular injection. In particular, the described invention provides for the promotion of the entry of a nutrient or a diagnostic or therapeutic agent across the blood-brain barrier by co-administering the agent with a hypertonic sugar composition, which sugar is administered by a route that permits absorption into the body through the nasal,

ocular, oral, otic rectal, vaginal, or upper respiratory mucosa, or through the skin or lungs. Specification pages 4-5.

35 U.S.C. §103(a)

Claims 1-10 and 12-28 stand rejected under 35 U.S.C. §103(a), as obvious in view of Naito and Keep.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). It is well-established that the conclusion that the claimed subject matter is prima facie obvious must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

According to the examiner, "Naito teaches ingesting substances with a combination of sugar and amino acid [hypertonic sugar composition] so that they coexist in the blood stream and result in the facilitation of the use of the added material by the body... The sugar/amino acid combination provides a vehicle and method for transporting substances across the blood-brain barrier (column 2, lines 2-4)." Answer, page 5. Naito exemplifies the administration of beta-carotene or xanthophylls with the sugar composition and indicates this composition has the effect of increasing the growth of hair and replacing grayness with original hair color. Id. Naito also teaches that any

non-carcinogenic material having apparent utility in connection with the treatment of the disorder being investigated may be combined with the hypertonic sugar composition. Id.

According to the examiner, "Naito teaches oral administration of hypertonic sugar compositions which is but one non-enteral or non-intravascular mode of administration." Answer, page 6.

Keep is relied on by the examiner for the disclosure of cyclosporins which cross the blood-brain barrier with the aid of osmotic agents for example, mannitol and arabinose and saccharose solutions, which are able to temporarily disrupt the blood-brain barrier and allow therapeutic delivery of the drug to the brain. Answer, page 6; Keep, column 5, lines 35-42. According to the examiner, suitable modes of administration described in Keep are "oral, sublingual, buccal, nasal, inhalation, parenteral, intraorgan, subcutaneous," etc. Answer, page 6.

The examiner concludes (Answer, pages 6-7):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer or sequentially administer the hypertonic sugar composition of Naito along with a chemical compound in order to increase the effectiveness of said compound, to increase the passage of the compound through or across the blood brain barrier, or to increase the permeability of the blood-brain barrier by a route other than enteral or intravascular injection since Keep teaches the use of hypertonic sugar compositions for passing therapeutic agents across the blood-brain barrier. The mode of administration is not seen to be a critical limitation that would lend patentability of the instantly claimed process over the prior art. The mode of administration is seen to be a choice of experimental design as the art teaches suitable alternatives. One of ordinary skill in the art would have been motivated to modify the teachings of Naito in order to treat traumatic brain damage.

The appellant responds, arguing Naito or Keep do not disclose any route of administration of a sugar composition to open the blood-brain barrier than oral (Naito) or intravascular (Keep). Brief, page 13.

With respect to Naito, appellant argues that "[t]he oral administration disclosed by Naito ... is by ingestion, that is by swallowing followed by absorption in the small intestines. Thus, the oral administration of Naito is an 'enteral (i.e. intestinal) administration.'" Reply Brief, page 2. Appellant further argues that the "present specification, at each instance where it discloses 'oral', refers to absorption through the oral mucosa, such as occurs when a subject sucks on a lozenge or gargles or chews gum." Reply Brief, page 2. Appellant argues claim 10 does not call for oral administration, but for administration via one of 6 different mucosal surfaces, one of which may be the oral mucosa. Id.

Appellant argues that, "Keep does not disclose any method of osmotic disruption of the blood-brain barrier other than by administration of a hypertonic osmotic agent by an intravascular route, either intra-arterial or intra-venous." Id. Instead Keep describes alternative modes of administration for only the formulary drug.

In addressing the appellant's arguments, the examiner submits that "[o]ral administration of the hypertonic composition [in Naito] meets the instant requirement of administration by a route other than enteral administration or intravascular injection (see claim 10)." Answer, page 8.

We disagree. When the claims are viewed in accordance with the specification and the prosecution history they encompass absorption through the oral mucosa and specifically exclude enteral and intravascular administrations. We agree with appellant that Naito does not describe administration of the sugar composition by a method other than enteral or intravascular. In our view, Naito's oral administration by ingestion reasonably appears to be enteral administration.[1] The examiner provides no evidence that administration by ingestion as described by Naito would not have been considered enteral administration by one of ordinary skill in the art. Moreover, we do not find that Keep overcomes the deficiencies of Naito, as Keep only describes intravascular administration of the sugar composition.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). See also, MPEP § 2143.03. We do not find the examiner has presented evidence of knowledge in the art of administration of the

---

[1] The Merck Manual of Diagnosis and Therapy, Section 22, Chapter 298 (2004), states that "For oral administration, the most common route, absorption refers to the transport of drugs across membranes of the epithelial cells in the GI tract. .... The oral mucosa has a thin epithelium and a rich vascularity that favors absorption, but contact is usually too brief, even for drugs in solution, for appreciable absorption to occur. A drug placed between the gums and cheek (buccal administration) or under the tongue (sublingual administration) is retained longer so that absorption is more complete." (Attached)

claimed sugar composition, through a method of administration other than enteral or intravascular, i.e. through the oral or other mucosa.

The examiner cannot rely on lack of criticality or experimental design as a basis for rejection of a positive claim limitation. Patent examiners, in relying on what they assert to be general knowledge to negate patentability on the ground of obviousness, must articulate that knowledge and place it of record, since examiners are presumed to act from the viewpoint of a person of ordinary skill in the art in finding relevant facts, assessing the significance of prior art, and making the ultimate determination of the obviousness issue. Failure to do so is not consistent with either effective administrative procedure or effective judicial review. Examiners cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which they rely. See In re Lee, 277 F.3d 1338, 1343-1344, 61 USPQ2d 1430, 1433-1434 (Fed. Cir. 2002). Thus, it is improper to rely on the “common knowledge and common sense” of a person of ordinary skill in art to find an invention obvious over a combination of prior art references, since the factual question of motivation to select and combine references is material to patentability, and cannot be resolved on subjective belief and unknown authority. In re Lee, 277 F.3d 1338, 1343-1344, 61 USPQ2d 1430, 1433-1434 (Fed. Cir. 2002).

As with every case before the board, this board functions as a board of review, not a de novo examination tribunal. 35 U.S.C. § 6(b) ("The [board] shall . . . review adverse decisions of examiners upon applications for patents . . .."). Each appeal

comes to the board with a unique record. On this record, we are constrained to find that the examiner has not provided sufficient evidence to support a prima facie case of lack of obviousness.

The dissent would appear to acknowledge the deficiencies of the record before us, noting that, to the extent that further explanation of the strengths of the prior art (and any de novo review by the board to establish a prima facie case of obviousness) "diverges from the examiner's reasons, that the support for the examiner's position, could, at the very least, have been denominated as a new ground of rejection."

We respectfully disagree. First, this board serves statutorily as a board of review, not a de novo examination tribunal. This administrative scheme necessarily preserves an appellant's right to cross-examine any arguments and prior art cited by the examiner and limit the appeal record in a manner appropriate for appellate review. While the majority acknowledges the board has regulatory authority to enter a new ground of rejection when warranted, we do not agree with the dissent that this is an appropriate case for the exercise of such authority.

What is clear from the record is that the blood-brain barrier exists and is due to a unique capillary structure in the brain. According to the specification and the prior art, the existence of the blood-brain barrier effectively prevents substances such as hormones, proteins, certain ions, and drugs from entering the brain without facilitated transport or lipid mediated transport. Keep acknowledges that, to some extent, what crosses the blood brain barrier is also dependent upon the nature of the compound.

Keep states that highly lipid soluble drugs cross the blood brain barrier easily. Column 4, lines 49-50. Keep acknowledges that "mechanisms for opening the blood brain barrier are known and include administration of hypertonic solutions intra-arterially & intravenously..." Column 4, lines 50-52. Naito also acknowledges these known methods for opening the blood brain barrier, and in addition finds that ingestion (enteral administration) of pure sugars in combination with amino acids can open the blood brain barrier. Thus, while drugs to be delivered to other parts of the body may be administered by a variety of known routes of administration, the brain may be unique in this respect, due to the relative impenetrability of the blood brain barrier.

The state of the art would thus appear to indicate that the ability of compounds to cross the blood-brain barrier is dependent upon a number of variables, including the nature of the chemical or compounds administered, and arguably, the prior art recognizes only limited modes of administration of the hypertonic sugar composition. While we believe it can be concluded from the prior art that administration of a hypertonic sugar composition enterally, intra-arterially or intravenously is effective in disruption of the blood brain barrier, we do not agree with either the examiner or our colleague that the examiner has presented argument based on evidence of record which would support the position that one of ordinary skill in the art would necessarily conclude that all modes of administration of a hypertonic sugar composition which eventually reach the blood stream, result in a sufficient opening of the blood brain barrier for a sufficient amount of time to allow other therapeutic compounds to cross.

While other modes of administration mentioned in Keep may be ready alternatives for administration of drugs or treatment compounds (distinguished and distinct from the hypertonic sugar solution) to other parts of the body, it would appear clear from the record that the blood brain barrier is recognized by those of ordinary skill in the art as being unique and distinct from other body tissues. Contrary to the dissent's characterization of Keep, we do not find Keep states that the hypertonic sugar composition may be administered by any mode of administration.

Furthermore, we note that unlike enteral absoprtion, contact is usually too brief with the oral mucosa, even for drugs in solution, for appreciable absorption to occur. Moreover, it is known from evidence of record that even with intravenous injection, the blood brain barrier may be open from as little as 20 minutes to 2 hours. Keep, column 5, line 45. While the dissent views the statement from the Merck Manual as demonstrating that persons having ordinary skill in the art understood that administration of a pharmaceutical composition to the sublingual, buccal and nasal mucosa was simply an alternative route of administering a composition to the blood stream, we do not find that the statement provides acknowledgment that any composition entering the blood stream by such routes would necessarily be of sufficient chemical composition or nature or in sufficient amounts to open the blood-brain barrier for a sufficient amount of time to allow entry of a therapeutic drug, administered by another means. Therefore, we disagree with the dissent on this point and do not view the evidence of record, without more, readily supports imposing a regulatory new

ground of rejection by the board.

In view of the above, we do not find the examiner has established a prima facie case of obviousness on the evidence before us. The rejection of claims 1-10 and 12-28 under 35 U.S.C. §103(a), as obvious in view of Naito and Keep is reversed.

CONCLUSION

The rejection of claims 1-10 and 12-28 under 35 U.S.C. §103(a), as obvious in view of Naito and Keep is reversed.

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

REVERSED

	)	
WILLIAM F. SMITH	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
DEMETRA J. MILLS	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	

ELLIS, Administrative Patent Judge, dissenting.

Contrary to the majority, I find some merit in the examiner's position. While the examiner has not fully capitalized on the strengths of the applied prior art, I do not feel it necessary to reverse the rejection. In my view, the examiner's position, as is most often the case given different perspectives and opinion, is in need of further explanation. To the extent that such explanation diverges from the examiner's reasons, the support for the examiner's position could, in the very least, have been denominated as a new ground of rejection.

A determination of obviousness is based on several factual inquiries concerning (i) the scope and content of the prior art, (ii) the level of ordinary skill in the art, (iii) the differences between the claimed invention and the prior art, and
(iv) secondary considerations of nonobviousness, such as commercial success, failure of others, unexpected results, etc. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). It is well established, as pointed out by the majority, that the examiner sustains the initial burden of establishing a prima facie case of obviousness. Pro-Mold &Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). In this regard, there must be some teaching in the art, or knowledge generally available in the art, that would lead one having ordinary skill in the art to combine the relevant teachings of the references. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). "The motivation, suggestion or teaching may come explicitly from the statements in the prior art, the knowledge of one of ordinary skill in

the art, or, in some cases the nature of the problem to be solved." In re Kotzab, 217 F.3d 1365, 1369, 55 USPQ2d 1313,1317 (Fed. Cir. 2000); Pro-Mold &Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d at 1573, 37 USPQ2d at 1630. In this case, I find that the suggestion to arrive at the claimed invention arises primarily from the latter two, i.e., from knowledge of those having ordinary skill in the art and the nature of the problem to be solved.

Here, I find that all parties, the examiner, the appellant and the majority, are in agreement that both Naito and Keep evince that the use of hypertonic sugar compositions to increase the permeability of the blood-brain barrier for passage by other compounds was known in the art at the time the application was filed. To that end, the examiner points out that Naito discloses that a hypertonic sugar solution provides "a vehicle and a method for transporting substances across the blood brain barrier." Answer, p. 5, pointing to Naito, col. 2, lines 2-4. The examiner further points out similar teachings in Keep. Answer, p. 6 relying on Keep col. 5, lines 35-42 and col. 6, lines 29-33. The applied prior art also discloses that the hypertonic sugar composition can be administered "in combination, simultaneously or in sequence" with the compound of interest (i.e., the compound/medication for which it is desired to treat the nervous system). Keep, col. 6, lines 29-33; Naito, col. 3, lines 39-50. Thus, the only difference between the claimed method and the methods taught by Naito and Keep is the route of administration of the hypertonic sugar composition. In this regard,

the examiner argues that the art teaches suitable alternatives for the mode of administration of said sugar composition. Answer, p. 7. I agree.

Turning to the applied prior art, I find that Keep discloses that hypertonic agents are typically "infused for 30 seconds through a major cerebral artery," but that less invasive and more convenient intravenous routes are also acceptable. Keep, col. 5, lines 42-44 and lines 49-52. Keep further discloses (col. 6, lines 29-33) that the invention includes

> . . . all methods of administering treatment medications along with all methods of opening, bypassing or disrupting the blood-brain barrier in combination, simultaneously or in sequence to get the treatment medication in contact with nervous tissues.

Keep still further discloses that numerous alternative routes of administering pharmaceutical compositions into the blood stream were known in the art at the time the application was filed. See, e.g., Keep, col. 5, line 64- col. 6, line 62. Keep still further discloses that the preferred route depends on the condition of the patient. Id., col. 6, lines 21-22. Keep still further discloses a formulation comprising a therapeutic drug (desired compound for crossing the blood-brain barrier) and mannitol (a sugar composition) which may be "isotonic, hypotonic or hypertonic with the blood of the recipient." Keep, e.g., col. 8, lines 59-66; see also, the Brief, p. 14, last para.

In addition to teaching that a hypertonic sugar composition increases the permeability of the blood-brain barrier, Naito discloses that the mode of administration is immaterial so long as the hypertonic sugar composition and compound of interest

coexist in the blood stream. Naito, col. 3, lines 46-50. This is because the site of action of the hypertonic sugar composition is in the bloodstream; said composition does not cross the blood-brain barrier. Naito, col, 3, lines 38-39. In addition, Naito discloses that the base material[2] can enter the blood stream either by ingestion or by direct introduction. Id., lines 35-38.

In my view, the aforementioned teachings of Keep and Naito would have suggested to one of ordinary skill in the art that any art-recognized method of inserting the hypertonic sugar solution into the blood stream (circulatory system) is acceptable for increasing the permeability of the blood-brain barrier. That is, it would have been obvious to one of ordinary skill in the art at the time of the present invention to employ any convenient route of administering the hypertonic sugar composition to increase the permeability of the blood brain barrier for passage by a therapeutic compound. In this regard, Keep demonstrates that there were many alternative routes known in the art by which pharmaceutical compositions could be introduced into the circulatory system, other than enterally or by intravenous injection, and that the various routes of pharmaceutical administration are interchangeable. See, e.g., Keep, col. 5, line 64-col. 6, line 62. Keep describes the use of alternative routes of administration with respect to the therapeutic drug as well as with the hypertonic sugar composition and a formulation comprising a therapeutic drug and sugar composition. See, col. 6,

[2] Naito defines the base composition as “a combination of the hypertonic sugar and amino acid which is effective to permit transportation of other materials into the glia of the brain past the blood brain barrier.” Naito, col. 3, lines 18-21.

lines 29-33 and col. 8, lines 59-66. Thus, Keep demonstrates that one of ordinary skill in the art would have understood at the time of the invention that (i) any pharmaceutical composition could be administered by any one of numerous alternative routes; and (ii) routes of administration through the sublingual, buccal or nasal mucosa, etc., are simply art-recognized alternative routes of inserting a pharmaceutical agent into the blood stream.[3] In sum, since Naito teaches that the site of action of the hypertonic sugar composition is the blood stream, one of ordinary skill in the art would have understood that any art-recognized route of administering said composition into the blood stream would be appropriate. Such persons select the route based on the condition of the patient (Keep, col. 6, lines 21-22) and the timing necessary to ensure that said composition and the therapeutic compound of interest are present in the blood stream at the same time (Naito, col. 3, lines 46-50). Thus, contrary to the majority, I find that the applied prior art demonstrates both the knowledge available in the art with respect to the administration of pharmaceutical compositions and how persons with said knowledge resolved the problems presented with different patients.

---

[3] As further evidence of the knowledge generally available in the art at the time of the appellants' invention, I direct attention to the Merck Manual relied upon by the majority. The manual states that the "oral mucosa is known for its thin epithelium and a rich vascularity that favors absorption." See attached, p. 3, para. 2. Thus, the manual demonstrates that persons having ordinary skill in the art understood that the administration of a pharmaceutical composition to the sublingual, buccal and nasal mucosa was simply an alternative routes of administering said composition to the blood stream.

Accordingly, in view of the teachings of Keep and Naito, I conclude that it would have been obvious to persons having ordinary skill in the art to increase the permeability of the blood-brain barrier by co-administering, or sequentially administering, a hypertonic sugar composition using any art-recognized route of administering a pharmaceutical composition to the bloodstream, which includes non-enteral [4] and non-injection intravenous routes, such as administration via the sublingual, buccal or oral mucosa, with a compound of interest. Moreover, in view of the teachings of Naito that the hypertonic composition is effective when administered orally,[5] one having ordinary skill in the art would have a reasonable expectation that administration of said composition via the sublingual, buccal, and nasal mucosa would be successful.

---

[4] Claim 10 lists several mucosa as routes of administration which include, inter alia, the rectal mucosa. According to the definitions of enteral administration found by the majority, rectal administration is a type of enteral administration which the claims are said to exclude. See, independent claim 1 on which claim 10 depends.

[5] Drugs which are administered orally, and which are absorbed by the gastrointestinal tract as opposed to the oral mucosa, risk degradation by digestive enzymes throughout the digestive tract prior to reaching the bloodstream. A hypertonic sugar composition administered orally in solution form as taught by Naito (col. 5, lines 45-47) must survive the transit time from the mouth throughout the digestive tract as well as encounters with low pH and potentially degrading enzymes. The Merck Manual, p. 3. Thus, the time between administration and absorption into the bloodstream of a hypertonic sugar composition which is administered orally is much greater than the time for absorption when said composition is administered directly by intravenous injection.

Obviousness does not require absolute predictability, only a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

JOAN ELLIS	)
Administrative Patent Judge	)

Appeal No. 2005-0126
Application No. 09/967,791

Howard Eisenberg, Esq.
2206 Applewood Court
Perkasi, PA 18944