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MEDTRONIC, INC. (NEURO/MRG)
710 MEDTRONIC PARKWAY NE
MS-LC340
MINNEAPOLIS, MN 55432-5604

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DICKINSON, PAUL W	

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rs.patents.five@medtronic.com

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DEEPAK RAMESH THAKKER,
LISA L. SHAFER, and GREG STEWART

Appeal 2018-007767
Application 13/267,243
Technology Center 1600

Before RICHARD M. LEBOVITZ, JEFFREY N. FREDMAN, and TAWEN CHANG, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a method of intrathecal molecule delivery to cerebrospinal fluid. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identify the Real Parties in Interest as Medtronic, Inc. and Medtronic, plc (*see* App. Br. 2).

[2] We have considered and refer to the Specification of Oct. 6, 2011 ("Spec."); Final Action of Sept. 21, 2017 ("Final Act."); Appeal Brief of Feb. 15, 2018 ("App. Br."); Examiner's Answer of May 29, 2018 ("Ans."); Reply Brief of July 24, 2018 ("Reply Br."); Prior Decision in Appeal 2015-004335 of Nov. 30, 2016 ("Dec.").

Statement of the Case

Background

"A variety of agents have been administered to the cerebrospinal fluid (CSF), such as through intracerebroventricular (ICV) or intrathecal (IT) bolus infusion. Typically, these agents are administered acutely through a single, bolus infusion at flow rates in the range of about 0.5 to 12 ml/min." (Spec. ¶ 3). "However, at lower flow rates, such as less than 1 ml/day, studies report that the distribution of the agent in the CSF is limited" (Spec. ¶ 4). "[I]t would be desirable to administer an agent at a low flow rate to a subject's CSF; e.g. when using a chronically implanted infusion device, but achieve broad distribution of the agent in the subject's CNS" (Spec. ¶ 5).

The Claims

Claims 1–6, 8–15, 17, 18, and 23–25 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method comprising:
> selecting a subject for which delivery of a therapeutic or diagnostic molecule to cerebrospinal fluid (CSF) of a brain is desired; and
> administering a liquid formulation comprising the molecule to an CSP-containing intrathecal space of the subject at a flow rate of less than 500 microliters per hour, wherein the liquid formulation is administered for a period of time sufficient to reach a steady state concentration in CSF of the brain, and wherein the molecular weight of the molecule is less than 5 kDa, between 15 kDa and 200 kDa, greater than 200 kDa, or a polypeptide or anti sense DNA having a molecular weight of between 5 kDa and 15 kDa, and wherein the molecule is generally distributed throughout at least most of the CSF of the brain at therapeutically or diagnostically effective concentrations.

The Issue

The Examiner rejected claims 1–6, 8–15, 17, 18, and 23–25 under 35 U.S.C. § 103(a) as obvious over Heruth[3] (Ans. 3–5).

The Examiner finds:

> Heruth discloses a method for delivering a therapeutic molecule to the cerebrospinal fluid of a brain of a subject, comprising administering a liquid formulation comprising the molecule to an CSF-containing intrathecal space, such as the lumbar space (paragraph 180), the thoracic space (paragraph 123), or the cervical space (paragraph 180), of the subject at a flow rate of less than 50 milliliters (50,000 microliters) per hour, wherein the liquid formulation is administered for 5 minutes or more (paragraph 37).

(Ans. 3). The Examiner finds "[l]ower flow rates yield more equitable drug distribution radially for both hypobaric and hyperbaric drugs (paragraph 136)" (Ans. 3). The Examiner finds:

> Regarding the limitation, "wherein the molecule is generally distributed throughout at least most of the CSF of the brain at therapeutically or diagnostically effective concentrations," the drug (molecule) of Heruth is administered to the spinal cord so as to reach the reach the CSF of the brain at therapeutically effective concentrations (paragraph 180). This is a teaching that the drug is distributed in the CSF of the brain at therapeutically effective concentrations. Although Heruth does not use the word "generally distributed," it would be understood that as the drug is solubilized in the CFS fluid of the brain in a therapeutically effective amount, and as it solubilized in the CFS fluid of the brain in a therapeutically effective amount, it would be generally distributed throughout at least most of the CSF of the brain.

(Ans. 4–5).

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[3] Heruth et al., US 2004/0220546 A1, published Nov. 4, 2004.

The Examiner found that Heruth describes delivery of morphine, a therapeutic molecule within the scope of the claim. The Examiner acknowledges that "Heruth fails to teach an example where morphine is delivered at a 'flow rate of less than 500 microliters per hour ... for a period of time sufficient to reach a steady state concentration in CSF of the brain'" (Ans. 3–4).

The Examiner finds that during "the course of optimizing the method for maximum efficacy and equitable drug distribution radially, the artisan would find the instant flow rate of less than 500 microliters per hour through routine experimentation" (Ans. 4).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Heruth renders the claims obvious?

Findings of Fact

1. Heruth teaches "a method for delivering a drug to a subject's brain via the subject's spinal canal. The method comprises administering . . . a hypobaric solution comprising the drug to the subject's cerebrospinal fluid (CSF) in a spinal location" (Heruth ¶ 180).

2. Heruth teaches

> The drug may enter the brain through CSF, as there is communication between CSF in the brain and in the spine. Infusing a hybobaric drug into a subject's spinal CSF may facilitate delivery of the drug the brain. As people sit and stand upright, buoyant forces will carry the drug upward towards the brain

(Heruth ¶ 180).

3. Heruth teaches "[i]n an embodiment, the drug or solution carrying the drug is sufficiently hydrophilic that the drug may reach the brain in a concentration effective to treat a disease" (Heruth ¶ 180).

4. Heruth teaches:

> [I]nfusing the drug solution to an internal body location at a continuous rate of no more than 50 milliliters (ml) per hour for a period of five minutes or more. In variations on this method, the maximum infusion rate may be, e.g., no more than 25 ml per hour, no more than 10 ml per hour, no more than 5 ml per hour, or even potentially ***no more than 2 ml*** [i.e. 2,000 µl] ***per hour***. Variations may also be found in the time period over which the infusion is performed. The period of infusion may alternatively be, e.g., 10 minutes or more, one hour or more, eight hours or more, or even 24 hours or more.

(Heruth ¶ 37; emphasis added).

5. Heruth teaches "[w]ith respect to the rate of infusion, low rates of infusion may tend to yield more equitable drug distribution radially for both hypobaric and hyperbaric drugs. Faster flow rates may lead to broader drug distribution over more vertebral segments than slower flow rates" (Heruth ¶ 136).

6. Heruth teaches

> if it is desirable to reach a variety of levels of a spinal column with drug, the flow rate with which the drug is delivered may be increased. . . . If it is desired to have a drug localized to a region around a particular level of the spinal column, the flow rate with which the drug is delivered may be decreased.

(Heruth ¶ 136).

7. Heruth teaches "[e]xemplary opioid agonists include morphine and hydromorphone. Ranges of effective daily doses of such drugs are known by physicians" (Heruth ¶ 172).

8. The Examiner finds that morphine has "a molecular weight of less than 5 kDa" (Final Act. 6).

Principles of Law

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

Analysis

Appellant "does not agree that Heruth reasonably teaches or suggests that intrathecal administration of a flow rate of less than 500 microliters per hour would result in the drug being generally distributed throughout at least most of the CSF of the brain at therapeutically or diagnostically effective concentrations" (App. Br. 7). Appellant contends instead that the "cited portions of Heruth teach or suggest that lower infusion rates lead to the drug tending to remain in a ring at a particular vertebral level (radially distributed) rather than being distributed more broadly over several vertebral segments (longitudinally distributed)" (App. Br. 9). Appellant further explains that "based on the teachings of Heruth, one would expect that a drug administered at a low flow rate would spread out radially at the vertebral level at which it was administered, but would not be expected to spread longitudinally to other vertebral levels" (App. Br. 10).

The Examiner responds that:

> Regarding the limitation, "wherein the molecule is generally distributed throughout at least most of the CSF of the brain at therapeutically or diagnostically effective concentrations," the drug (molecule) of Heruth is administered to the spinal cord so

> as to reach the reach the CSF of the brain at therapeutically effective concentrations (paragraph 180). This is a teaching that the drug is distributed in the CSF of the brain at therapeutically effective concentrations. Although Heruth does not use the word "generally distributed," it would be understood that as the drug is solubilized in the CFS fluid of the brain in a therapeutically effective amount, and as it solubilized in the CFS fluid of the brain in a therapeutically effective amount, it would be generally distributed throughout at least most of the CSF of the brain.

(Ans. 4–5).

We find that Appellant has the better position. Unlike the previous appeal, where we noted that "'broad distribution of the drug in CSF' is not a limitation of claim 1" (Dec. 6), the instant claims on appeal all include a limitation that the therapeutic molecule is "generally distributed throughout at least most of the CSF of the brain." And as Appellant notes, Heruth does not support the idea that lower drug amounts will result in general distribution in the CSF. Thus, while Heruth discloses amounts less than 2 ml, the skilled worker would not have had reason to use 500 microliters or less because it would defeat the purpose described by Heruth. Rather, Heruth teaches that:

> if it is desirable to reach a variety of levels of a spinal column with drug, the flow rate with which the drug is delivered may be increased. . . . If it is desired to have a drug localized to a region around a particular level of the spinal column, the flow rate with which the drug is delivered may be decreased.

(FF 6). Heruth therefore teaches that reduction of the flow rate results in localization of drug delivery, not a broad distribution in the CSF as taught by Appellant. This is a teaching away because it leads "in a direction divergent from the path that was taken by the applicant." *Gurley*, 27 F.3d at 553. The

Examiner provides no evidence, as opposed to argument, that Heruth's delivery would necessarily be "generally distributed" in the brain.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Heruth renders the claims obvious.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
1–6, 8–15, 17, 18, 23–25	103	Heruth		1–6, 8–15, 17, 18, 23–25

REVERSED