

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Edward T. Maggio	Art Unit:	1649
Application No.:	13/371,274	Examiner:	Borgeest, Christina M.
Filed:	February 10, 2012	Conf. No.:	3112
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP RCE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Dr. Edward T. Maggio, do hereby declare and state that:

1. I am named as an inventor on U.S. Patent Application Serial No. 13/371,274 and am currently Chief Executive Officer and Director of Aegis Therapeutics, LLC.

2. I hold a B.S. in Chemistry from Polytechnic University, a Ph.D. degree in Biochemistry from the University of Michigan, and was a National Institute of Health postdoctoral fellow at the University of California, San Francisco in the Department of Pharmaceutical Chemistry. I consider myself to be an expert in the field of pharmaceutical chemistry and in particular in the area of pharmaceutical formulations.

3. I am familiar with the contents of the above-identified application, and have reviewed the Office Action dated April 10, 2013. I understand that the Examiner has rejected claims 7, 9-15, 17 and 18 under 35 U.S.C. §103, as allegedly obvious over Meezan et al. (U.S. Patent No. 5,661,130; hereinafter 'Meezan') in view of Lahat et al. (*The Lancet*, 1998; 352:620; hereinafter 'Lahat'); and claim 16 under 35 U.S.C. §103, as allegedly obvious over Meezan in view of Lahat and further in view of Frey (U.S. Pat. App. Pub. No. 2002/0141971; hereinafter 'Frey').

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4. I am familiar with and have generally reviewed the references cited in the Office Action, in particular, Meezan, Lahat and Frey.

5. The present invention is based on the discovery that the alkyl glycoside, dodecyl- β -D-maltoside (also referred to as n-dodecyl- β -D-maltoside), increases absorption of therapeutic agents to the cerebral spinal fluid (CSF) of the central nervous system (CNS) of a subject upon nasal administration.

6. In Appendix A, the absorption increasing activity of certain alkylglycosides as well as other agents were analyzed. The experiment described was performed under my general direction and guidance. As described in Appendix A, formulations including a therapeutic agent (*Homo sapien* derived antibody Fc fragment (hFc)) and various compounds including dodecyl- β -D-maltoside were compared. As shown in Table 1, nasal administration of formulations comprising therapeutic agent (hFc) and 0.5% (w/v) -n-dodecyl- β -D-maltoside to isoflurane anesthetized animals resulted in therapeutic agent concentrations in CNS tissues that were increased relative to other alkyl glycosides as well as other agents that were tested, particularly n-decyl- β -D-maltoside. Surprisingly, a near 200% increase in CNS absorption, *e.g.*, absorption through the CSF, was determined for dodecyl- β -D-maltoside as compared to decyl- β -D-maltoside.

7. One of ordinary skill in the art would appreciate the significance of the experimental results presented in Appendix A. The determination that dodecyl- β -D-maltoside exhibits nearly a two fold increase in CNS absorption as compared to decyl- β -D-maltoside, an alkyl glycoside which differs in alkyl length by only 2 carbons from dodecyl- β -D-maltoside, is indeed surprising and unexpected. Further, one would expect to observe a similar increase in absorption by dodecyl- β -D-maltoside for other therapeutic agents, such as anti-seizure agents.

In re Application of:

Edward T. Maggio

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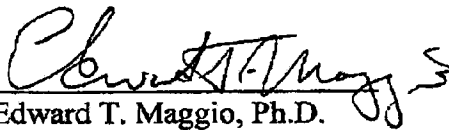
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Attorney Docket No.: AEGIS1210-14

Even more significant is that such unexpected results are achieved at concentrations of dodecyl- β -D-maltoside at which acceptable levels of cytotoxicity are preserved.

8. I further declare that the statements made herein of my own knowledge and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 19Sept2013


Edward T. Maggio, Ph.D.

Experiment: Nasal Administration of Dodecyl- β -D-maltoside and Therapeutic Agent

In this experiment, the ability of various agents to deliver a therapeutic agent to the central nervous system (CNS) including the cerebral spinal fluid (CSF) via nasal administration was tested. Nasal administration of a *Homo sapien* derived antibody Fc fragment (hFc) to CNS tissues was increased, relative to control hFc formulations, by inclusion of the compounds listed in Table 1.

Table 1: Antibody hFc formulations that increase antibody fragment delivery to central nervous system tissues, relative to control hFc formulations, in isoflurane anesthetized animals.

Compound Identity and Quantity in PBS (pH 7.4) Diluent Based Formulations Containing 36 mg/ml hFc		Mean Fold Increase* in Brain Delivery Efficiency of hFc after Nasal Administration of Formulation
Compound Identity	Quantity	
n-dodecyl- β -D-maltoside	0.5% (w/v)	7.6 (n=21)
n-decyl- β -D-maltoside	0.5% (w/v)	4.3 (n=7)
propylene glycol	10-20% (v/v)	4.5 (n=13)
heptakis(2,6-di-O-methyl)-beta-cyclodextrin	5% (w/v)	3.1 (n=8)
Sodium tauroursodeoxycholate	1% (w/v)	4.0 (n=6)

* represents mean fold increase in brain delivery efficiency (DE) of nasally administered hFc relative to control formulation (PBS; pH 7.4 and 36 mg/ml hFc)

A rat model was used for evaluating intranasal drug delivery to the brain. Male Sprague-Dawley rats were anesthetized with 3.0% isoflurane inhalant to facilitate nasal administration of the liquid formulations comprising hFc. Anesthetized rats were placed on their backs and their necks and head were supported with a platform to elevate their heads at a 45° angle. A micro-cannula was then inserted 1 cm into the right nostril of the animals and a 50 µL bolus of the liquid formulations was administered over the span of 1 minute. A heating pad was used to maintain body temperature of anesthetized animals.

20 minutes after nasal administration of the hFc formulations, animals were perfused via cardiac puncture with phosphate buffered saline (PBS) containing protease inhibitors (1 Roche protease inhibitor cocktail tablet per 10 ml of PBS) and 5 nM EDTA tetrasodium salt. Brains, blood and other tissues were then dissected, collected, and analyzed for hFc content.

Control hFc formulations comprised 36 mg/ml hFc in PBS at pH 7.4. The formulations described in Table 1 above each contained an absorption compound in the quantity indicated in the Table. Formulations were made using PBS at pH 7.4 as the diluent and contained a final hFc concentration of 36 mg/ml.

As seen in Table 1, nasal administration of hFc formulations comprising 0.5% (w/v) -n-dodecyl-β-D-maltoside to isoflurane anesthetized animals resulted in hFc concentrations in CNS tissues that were increased relative to other alkyl glycosides tested (e.g., n-decyl-β-D-maltoside) and isoflurane anesthetized animals receiving the control hFc formulation in PBS only. A near

200% increase in absorption is shown for n-dodecyl- β -D-maltoside as compared to n-decyl- β -D-maltoside.