



No. 11-009141-00001-0000

Fecha: 2011-02-09 14:54:04 Dep. 2020 DIR.NUEVASCR
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COLOMBIA

P-2816

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref.: Expediente No. 11.009.141
Solicitud de Patente a nombre de
CODMAN & SHURTLEFF, INC.

Yo, DILIA MARÍA RODRÍGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **CODMAN & SHURTLEFF, INC.** domiciliada en Raynham, Massachusetts, Estados Unidos, solicitante de la patente de la referencia, atentamente me permito presentar:

1. Documento (1) en que consta la cesión del derecho a la patente otorgada por los inventores a favor de mi mandante.

Sobre el particular, es importante resaltar que de conformidad con las normas legales vigentes, artículo 1 de la Resolución 210 de 2001, expedida por el Superintendente de Industria y Comercio y artículo 2 de la Convención de la Haya, el documento en inglés que se pretenda aportar como parte de los trámites de propiedad industrial ante la Superintendencia de Industria y Comercio no requieren traducción. Por otro lado, la legalización consular y/o diplomática de los documentos expedidos en el extranjero no es necesaria. Por lo tanto, el documento de cesión anexo a este memorial es válidamente presentado en idioma inglés y con la correspondiente apostilla.

2. Copia certificada de la solicitud de Patente número 12/696,588 de Enero 29 de 2009, con la debida traducción de lo pertinente.

DILIA MARÍA RODRÍGUEZ D'ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824 CSJ

Robert M. M.

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by *W. Montgomery*

3. acting in the capacity of *Certifying Officer*

4. bears the seal/stamp of *U.S. Patent and Trademark Office*

Certified

5. at Washington, D.C.

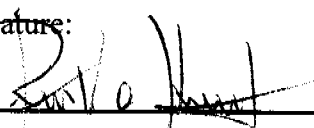
6. the *third of February, 2011*

7. by *Assistant Authentication Officer, United States Department of State*

8. No. *11915032-7*

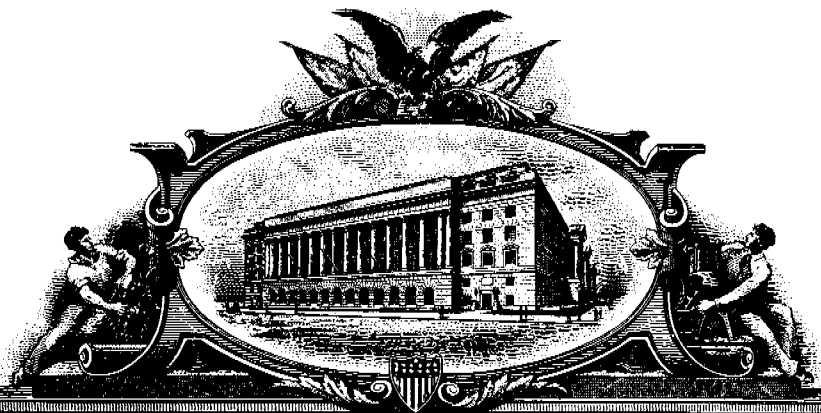
9. Seal/Stamp:

10. Signature:



Patrick O. Hatchett

A 7278321



THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 31, 2011

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FEBRUARY 23, 2010.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office



W. Montgomery
W. MONTGOMERY
Certifying Officer

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT										
NATURE OF CONVEYANCE:	ASSIGNMENT										
CONVEYING PARTY DATA											
<table border="1"> <thead> <tr> <th>Name</th> <th>Execution Date</th> </tr> </thead> <tbody> <tr> <td>Thomas M. DiMauro</td> <td>02/11/2010</td> </tr> <tr> <td>Alan Dextrateur</td> <td>02/11/2010</td> </tr> <tr> <td>Sean Lilienfeld</td> <td>02/11/2010</td> </tr> <tr> <td>Ramakrishna Venugopalan</td> <td>02/11/2010</td> </tr> </tbody> </table>		Name	Execution Date	Thomas M. DiMauro	02/11/2010	Alan Dextrateur	02/11/2010	Sean Lilienfeld	02/11/2010	Ramakrishna Venugopalan	02/11/2010
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RECEIVING PARTY DATA											
<table border="1"> <tr> <td>Name:</td> <td>Codman & Shurtleff, Inc.</td> </tr> <tr> <td>Street Address:</td> <td>325 Paramount Drive</td> </tr> <tr> <td>City:</td> <td>Raynham</td> </tr> <tr> <td>State/Country:</td> <td>MASSACHUSETTS</td> </tr> <tr> <td>Postal Code:</td> <td>02767</td> </tr> </table>		Name:	Codman & Shurtleff, Inc.	Street Address:	325 Paramount Drive	City:	Raynham	State/Country:	MASSACHUSETTS	Postal Code:	02767
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PROPERTY NUMBERS Total: 1											
<table border="1"> <thead> <tr> <th>Property Type</th> <th>Number</th> </tr> </thead> <tbody> <tr> <td>Application Number:</td> <td>12696588</td> </tr> </tbody> </table>		Property Type	Number	Application Number:	12696588						
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CORRESPONDENCE DATA											
Fax Number: (732)524-2808 <i>Correspondence will be sent via US Mail when the fax attempt is unsuccessful.</i> Phone: 732-524-6956 Email: JNJUSPATENT@CORUS.JNJ.COM Correspondent Name: Philip S. Johnson Address Line 1: One J&J Plaza Address Line 4: New Brunswick, NEW JERSEY 08933											
ATTORNEY DOCKET NUMBER:	COD5222USCIP1										
NAME OF SUBMITTER:	Crystal Washington										
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Serial No. 12/696,588
Filing Date: 01/29/2010

DOCKET NO. COD5222USCIP1
Joint Inventors

ASS I G N M E N T

WHEREAS, Thomas M. DiMauro, Alan Dextradeur, Sean Lilienfeld and Ramakrishna Venugopalan, residing at 3 Fitzgerald Lane, Southborough, MA 01772, 15 Lyons Street, Franklin, MA 02038, 12 Terrapin Lane, Sharon, MA 02067 and 15 Old Cart Path, Holliston, MA 01746 respectively (hereinafter called "Assignors"), have made certain new and useful inventions or discoveries relating to

Shunt Delivery of Curcumin

for which they have on January 29, 2010 filed an application for Letters Patent of the United States, identified as Serial No. 12/696,588; and

WHEREAS, CODMAN & SHURTLEFF, INC., a corporation of the State of New Jersey, (hereinafter called "Assignee") is desirous of acquiring Assignors' entire right, title, and interest therein:

NOW, THEREFORE, BE IT KNOWN that for good and valuable considerations, the receipt of which is hereby acknowledged, Assignors have sold, assigned, and transferred, and do hereby sell, assign and transfer unto said Assignee their entire right, title and interest in and to all said inventions and discoveries disclosed in said application whose identification above by serial number and filing date, when available is hereby authorized, and in and to said application, all substitutions, non-provisionals, divisions, and continuations thereof, and in and to all Letters Patent, United States and foreign, that may be granted for said inventions and discoveries, and in and to all extensions, renewals, and reissues thereof, the same to be held and enjoyed by said Assignee, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by Assignors if this Assignment and sale had not been made;

And Assignors hereby authorize and request the Commissioner of Patents of the United States to issue said Letters Patent in accordance with this Assignment;

And for the consideration aforesaid, Assignors covenant and agree with said Assignee that he has a full and unencumbered title to the inventions and discoveries above

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described and hereby assigned, which title they warrant unto said Assignee, its successors and assigns;

And for the consideration aforesaid, Assignors further covenant and agree that they will, whenever requested, but without cost to them promptly communicate to said Assignee or its representatives any facts known to them relating to said inventions and discoveries, testify in any interference or legal proceedings involving said inventions and discoveries, and execute any additional papers that may be necessary to enable said Assignee or its representatives, successors, nominees, or assigns to secure full and complete protection for the said inventions and discoveries or that may be necessary to vest in said Assignee the complete title to the said inventions and discoveries and patents hereby conveyed and to enable it to record said title.

IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 11 day of February, 2010

Thomas M. DiMauro (L.S.)
Thomas M. DiMauro

Alan Dextradeur (L.S.)
Alan Dextradeur

Sean Lilienfeld (L.S.)
Sean Lilienfeld

R. Venugopalan (L.S.)
Ramakrishna Venugopalan

STATE OF MASSACHUSETTS
) ss.
COUNTY OF BOSTON

BE IT REMEMBERED, That on this ^{if} day of February, 2010, before me, a Notary Public, personally appeared Thomas M. DiMauro, Alan Dextradeur, Sean Lilienfeld and Ramakrishna Venugopalan, who I am satisfied are the persons named in and who executed the foregoing instrument in my presence, and I having first made known to them the contents thereof, they did acknowledge that they signed, sealed, and delivered the same as their voluntary act and deed for the uses and purposes therein expressed.



AMY PELLETIER
Notary Public
Commonwealth of Massachusetts
My Commission Expires January 21, 2011

Amy Pelletier
Notary Public

RECORDED: 02/23/2010

PATENT
REEL: 023975 FRAME: 0316

ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Enero 24, 2011

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 12/696,588

Fecha de Presentación: Enero 29 de 2010

EL CÓDIGO DEL PAÍS Y EL NÚMERO DE SU SOLICITUD DE PRIORIDAD, PARA SER USADA EN LA PRESENTACIÓN EXTRANJERA BAJO EL CONVENIO DE PARÍS ES US 12,696,588

Por la autoridad de

Bajo el Secretario de Comercio para la Propiedad Intelectual y el Director de la Oficina de Patentes y Marcas de los Estados Unidos de América

(fdo) **W.MONTGOMERY**

Oficial Certificador

Sello oficial de la Oficina de Patentes y Marcas de los Estados Unidos de América



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January 24, 2011

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
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OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 12/696,588

FILING DATE: January 29, 2010

**THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY
APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS
CONVENTION, IS US12/696,588**

**By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office**

W. Montgomery
W. MONTGOMERY
Certifying Officer



Electronic Acknowledgement Receipt

EFS ID:	6911836
Application Number:	12696588
International Application Number:	
Confirmation Number:	1236
Title of Invention:	SHUNT DELIVERY OF CURCUMIN
First Named Inventor/Applicant Name:	Thomas M. DiMauro
Customer Number:	27777
Filer:	Eugene L Szczecina/Crystal Washington
Filer Authorized By:	Eugene L Szczecina
Attorney Docket Number:	COD5222USCIP1
Receipt Date:	29-JAN-2010
Filing Date:	
Time Stamp:	15:46:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$1142
RAM confirmation Number	2289
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:
 Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	ADS.pdf	907026 7767283e89f14902ea1ba46c3ace9e1be0f959e	no	5
Warnings:					
Information:					
2	Drawings-only black and white line drawings	COD5222USCIP1_DRGS.pdf	1497798 2912454009d068cc63715f10a9a86aa168699103	no	3
Warnings:					
Information:					
3	Specification	COD5222USCIP1_SPEC_Shunt DelivCurcumin_Appln.pdf	289158 5ca517dd43925a0150770c58706a20192d0ffc37	no	20
Warnings:					
Information:					
4	Oath or Declaration filed	COD5222USCIP1_DEC.pdf	1287838 3f67d67ccc1dc11c7cdc77c64f8118f0a67c1f89	no	8
Warnings:					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	36129 dacbf853b1b095dd67eb5b0a05cc5341a6ef0ea	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			4017949		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. New Applications Under 35 U.S.C. 111 If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. National Stage of an International Application under 35 U.S.C. 371 If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. New International Application Filed with the USPTO as a Receiving Office If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

SHUNT DELIVERY OF CURCUMIN

CROSS REFERENCE TO RELATED APPLICATION

The present application is a continuation-in-part of pending application United States Serial No.
5 12/359713, filed January 26, 2009.

BACKGROUND OF THE INVENTION

1. Field of the Invention

10 [0001] The invention relates to a method for delivering curcumin to a patient and more particularly to directing a curcumin agent intracranially to treat a human brain disorder such as Alzheimer's disease.

2. Description of the Related Art

15 [0002] Human brain tissue includes gray and white matter suspended in cerebrospinal fluid within the cranium and nourished by blood delivered through cerebral arteries. The gray matter has closely spaced cell bodies of neurons, such as in the cerebral cortex, and the underlying white matter contains densely packed axons that transmit signals to other neurons. Brain tissue has different densities and comprises approximately eighty percent of the intracranial content, with blood and cerebrospinal fluid each normally comprising approximately ten percent.

20 [0003] Cerebrospinal fluid is produced in several connected chambers known as ventricles and typically is renewed four to five times per day. Cerebrospinal fluid in a healthy human flows slowly and continuously through the ventricles, propelled by pulsations of the cerebral arteries, flows around the brain tissues and the spinal column, and then through small openings into the arachnoid membrane, which is the middle layer of the meninges surrounding the brain
25 parenchyma and ventricles, where the fluid is finally reabsorbed into the bloodstream.

[0004] There are a number of brain disorders that arise from neurotoxins or other pathogenic substances which can accumulate in cerebrospinal fluid. For example, it has long been recognized that aggregation of the protein amyloid-beta, which can be found in cerebrospinal fluid, contributes to the degenerative condition known as Alzheimer's disease. Microscopic

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damage to brain tissue leads to atrophy and a general decline in brain function known as dementia.

[0005] U.S. Patent No. 5,980,480 by Rubenstein et al. describe a method and apparatus for treating adult-onset dementia due to Alzheimer's disease, based on the premise that dysfunction of normal bodily processes can lead to deleterious materials being retained within cerebrospinal fluid. A portion of a patient's cerebrospinal fluid is removed at a controlled rate to encourage the patient's body to produce replacement cerebrospinal fluid and thereby dilute the concentration of any deleterious materials within the cranium. The withdrawn fluid is returned to a bodily space such as the peritoneal cavity. In one embodiment, a dialysate chamber is provided, its walls being coated with antibodies specific to target agents within the withdrawn cerebrospinal fluid. Alternatively, antibodies are bound to beads, strands or other structures that can be periodically exchanged within the dialysate chamber through a dialysate port.

[0006] In U.S. Publication No. 2009/0131850, Mark Geiger discloses an implanted pump and filter system having a drug or enzyme to clean and filter cerebrospinal fluid. One lumen of a dual lumen catheter withdraws cerebrospinal fluid into a drug and filter reservoir and the other lumen returns the treated fluid to the subarachnoid space of the patient.

[0007] An occlusion resistant hydrocephalic shunt is disclosed in U.S. Patent No. 7,582,068 by Koullick et al. having a proximal end located in brain tissue and a distal end located within the patient external to the brain or located external to the patient altogether. The proximal end of the shunt carries an occlusion resistant or anti-occlusion agent in drug eluting regions where clotting or tissue growth tend to occlude the lumen of the shunt. A great number of possible anti-occlusion pharmaceutical agents are listed including curcumin.

[0008] Curcumin has been applied to endovascular stents to reduce restenosis, such as disclosed in U.S. Publication 2008/0241352 by Shalaby.

[0009] The phenolic molecule curcumin is also known as diferuloylmethane or (E,E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5,-dione. Curcumin may be derived from a natural source, the perennial herb *Curcuma longa* L., which is a member of the Zingiberaceae family. The spice turmeric is extracted from the rhizomes of *Curcuma longa* L. and has long been associated with traditional-medicine treatments used in Hindu and Chinese medicine. Turmeric was administered orally or topically in these traditional treatment methods.

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[00010] Curcumin has been fed to and injected into the carotid artery of transgenic mice, as described by Yang et al. in "Curcumin Inhibits Formation of Amyloid Beta Oligomers and Fibrils, Binds Plaques, and Reduces Amyloid in Vivo", J. Biol. Chem. vol. 280, pp. 5892-5901 (2005). The article proposes conducting human clinical trials for curcumin to investigate whether curcumin may prevent or perhaps treat Alzheimer's disease.

[00011] It is therefore desirable to have a simpler, more rapid and more effective technique for reducing or eliminating pathogenic substances within human cerebrospinal fluid.

SUMMARY OF THE INVENTION

[00012] An object of the present invention is to provide a curcumin agent directly to cerebrospinal fluid for an extended period of time to attenuate the effects of a pathogenic substance on the brain of a human.

[00013] Another object of the present invention is to treat dementia by delivering a curcumin agent into the brain.

[00014] A further object of the invention is to allow continuous long-term delivery of a curcumin agent to areas of the body where targeted neurotoxins exist or could potentially form and thereby reduce or eliminate Alzheimer's-type dementia.

[00015] This invention results from the realization that at least one of curcumin, a curcumin hybrid and a curcumin analog delivered to a sub-dural or sub-meningeal location within the brain is likely to reduce or eliminate neurotoxins and other pathogens such as amyloid-beta to treat or prevent occurrence of a brain disorder, especially Alzheimer-type dementia. The terms curcumin, curcumin hybrid and curcumin analog are defined below. The term sub-dural as used herein is intended to include all tissues, fluids and spaces underlying the outermost layer of the dura mater of the meninges, and therefore includes intra-dural sinuses such as the superior sagittal sinus, as well as gray matter, white matter and the ventricles. The term sub-meningeal as used herein is intended to include everything underlying the pia mater, which is the innermost layer of the meninges; in other words, the term sub-meningeal excludes the arachnoid and dura mater membranes and any spaces or sinuses within them. The term brain

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parenchyma as used herein is intended to include gray matter, white matter and other essential parts of the brain providing its function.

[00016] This invention features a method by which a human brain disorder relating to the presence of a pathogenic substance in cerebrospinal fluid is reduced or prevented by selecting a human for treatment as a patient and placing a proximal end of a first catheter, having at least a first lumen, in a first sub-dural location within the brain of the patient to establish open communication between the first lumen and cerebrospinal fluid of the patient. For an extended period of time, a curcumin agent selected from at least one of curcumin, a curcumin hybrid and a curcumin analog is delivered to the cerebrospinal fluid to interact with the pathogenic substance to attenuate its effect on the brain.

[00017] In one embodiment, the patient is selected because he or she was diagnosed as having a brain disorder, preferably as having Alzheimer's disease for purposes of treatment according to the present invention. In a preferred embodiment, curcumin achieves a brain tissue concentration of at least 0.1 μM , more preferably at least 1 μM , more preferably at least 5 μM , more preferably at least 20 μM .

[00018] In some embodiments, the proximal end of the catheter is placed within a ventricle of the brain as the first sub-dural location, and cerebrospinal fluid intermixed with the curcumin agent is returned directly to the first sub-dural location. In some other embodiments, the cerebrospinal fluid intermixed with the curcumin agent is returned directly to another sub-dural location within the brain of the patient. The exposed cerebrospinal fluid is returned to the patient through a second lumen of the first catheter, or through a second lumen of a second catheter.

[00019] In a further embodiment, the curcumin agent is released from a reservoir connected to the first catheter. Preferably, the reservoir includes a removable canister carrying curcumin agent or is otherwise rechargeable so that additional curcumin agent can be added to extend the treatment period or increase the dosage of curcumin agent. In one embodiment, a proximal catheter connected to the reservoir transports cerebrospinal fluid intermixed with the curcumin agent to another location within the patient such as the peritoneal cavity. In another

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embodiment, the curcumin agent is released from a coating carried within at least a portion of the first catheter.

[00020] In yet another embodiment, the method further includes sampling cerebrospinal fluid at a sub-dural location that is different than the first sub-dural location and measuring the concentration of the curcumin agent in the cerebrospinal fluid to estimate its brain tissue concentration.

[00021] This invention may also be expressed as a system and method for reducing or preventing a human brain disorder relating to the presence of a pathogenic substance in cerebrospinal fluid by selecting a human for treatment as a patient and placing a proximal end of a first catheter, having at least a first lumen, in a first sub-dural location, preferably a sub-meningeal location, within the brain of the patient to establish open communication between the first lumen and cerebrospinal fluid of the patient. Cerebrospinal fluid is withdrawn through the first lumen and is exposed to a curcumin agent selected from at least one of curcumin, a curcumin hybrid and a curcumin analog to interact with the pathogenic substance to attenuate its effect on the brain. The exposed cerebrospinal fluid is returned to the patient so that the curcumin agent achieves a brain tissue concentration of at least 0.1 μ M.

BRIEF DESCRIPTION OF THE DRAWINGS

[00022] In what follows, preferred embodiments of the invention are explained in more detail with reference to the drawings, in which:

FIG. 1A is a perspective cross-sectional view of a patient showing a proximal catheter positioned in a ventricle within the brain of the patient according to one embodiment of the present invention;

FIG. 1B is a side cross-sectional view of a dual lumen Ommaya-type reservoir system for delivering a curcumin agent according to the present invention;

FIG. 1C is a perspective view of a delivery pump system according to another embodiment of the present invention; and

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FIGS. 1D-22 and FIG. 29 are incorporated by reference from U.S. Application No. 12/359,713 filed January 26, 2009 and entitled "Methylene Blue-Curcumin Analog for the Treatment of Alzheimer's Disease".

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DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

[00023] The term "curcumin agent" is described in more detail below. A portion of system 10 according to one aspect of the present invention is illustrated in FIG. 1A having a proximal catheter 12, a reservoir 14, and a distal catheter 16. A patient P is selected based on one or more criteria, such as having been diagnosed as having a brain disorder such as Alzheimer's disease. Reservoir 14 is implanted under the scalp of the patient P and a leading portion 18 of the proximal catheter 12, also referred to as a ventricular catheter in this construction, is placed through a burr hole 20 into a first sub-dural location such that inlet holes 22 of proximal end 24 communicate with cerebrospinal fluid in right ventricle RV. Alternatively, the proximal end 24 is placed in left ventricle LV or other sub-dural location, preferably sub-meningeal location, in communication with cerebrospinal fluid of patient P.

[00024] In this construction, catheter 12 defines at least a first lumen communicating with inlet holes 22 at proximal end 24 and with reservoir 14 at distal end 26. Cerebrospinal fluid is withdrawn through the first lumen and into reservoir 14, which includes a removable canister 28 having access port 30. Preferably, curcumin agent is loaded into canister 28 prior to implantation of system 10, and then dosage amounts of curcumin agent can be extended or increased by needle injection through access port 30. Canister 28 can also be removed and recharged or replaced as desired. Curcumin agent is delivered for an extended period of time to interact with one or more pathogenic substances to attenuate the effect of the pathogenic substance on the brain of the patient. Preferably, a desired brain tissue concentration of curcumin agent is achieved as described below.

[00025] Distal catheter 16 returns cerebrospinal fluid, exposed to curcumin agent according to the present invention, to another location within the patient P such as the peritoneal cavity. Alternatively, another lumen returns exposed cerebrospinal fluid to a sub-dural location

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such as shown in FIG. 1B for Ommaya-type system 40 according to another aspect of the present invention. First catheter 42 and second catheter 44 having lumens 46 and 48, respectively, are passed through burr hole 50 in skull S of patient P. In an alternative construction, lumens 46 and 48 are defined by a single catheter. Typically, proximal end 51 of first catheter 42 is placed in a first sub-dural location to withdraw cerebrospinal fluid and proximal end 53 is placed in a second sub-dural location, which can be the same or different space, tissue or region of the brain, to return exposed cerebrospinal fluid directly to the brain. In another construction, curcumin agent is simply delivered through lumen 48 into cerebrospinal fluid while other cerebrospinal fluid is withdrawn through lumen 46 for sampling and measuring purposes.

[00026] System 40 can be derived from or can utilize devices such as the Codman 3000 constant flow rate wound capillary tube device, with dosage of curcumin agent being increased by increasing its concentration as passed through the capillary tubes. Another device is the Archimedes device with etched chip having a tortuous path to define flow rate of delivered fluids. Both devices are currently commercially available from Codman & Shurtleff, Inc. of Raynham, Massachusetts.

[00027] As illustrated in FIG. 1B in partial side cross-sectional view, lumen 46 communicates with a first chamber 52 defined by dome wall 56 and lumen 48 communicates with a second chamber 54 defined by dome wall 58, which is separated from chamber 52 by septum 60. Dome walls 56 and 58 can be separately tactilely discerned and palpated to move fluid therethrough. In another construction as shown in phantom, septum 60 continues upward as septum 60' to a single dome wall 62 defining or covering both chambers 52 and 54. In either construction, a check valve can be provided to allow fluid to flow in only one direction between chambers 52 and 54 during palpation. A separate "squeeze-bulb"-type chamber can also be provided for mechanical or electro-mechanical activation as desired.

[00028] As further illustrated in FIG. 1B, system 40 in one construction includes multi-lumen catheter 70 defining a lumen 72 which communicates with chamber 52 and a lumen 74 which communicates with chamber 54 to enable fluid to be remotely withdrawn, delivered and/or returned separately and independently for each chamber 52, 54. A remote delivery pump 90 can be utilized such as shown in FIG. 1C to communicate with one or more lumens through catheter 92 implanted under the skin of patient P. One example of a suitable pump is the

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CODMAN Medstream pump with piezo-electric valve having a variable duty cycle which is currently commercially available from Codman & Shurtleff, Inc. of Raynham, Massachusetts. Other types of pumps or delivery devices can be utilized to provide curcumin agent directly to cerebrospinal fluid for days, weeks or months as desired according to the present invention.

5 [00029] Cerebrospinal fluid can be exposed to a curcumin agent according to the present invention in one or more reservoirs or by contact with a coating, a surface or a porous substrate containing curcumin agent. In one construction a hydrophilic, lipophobic membrane, preferably carried in a removable, replacable cartridge, traps a gel containing curcumin agent and allows only cerebrospinal fluid to flow therethrough. A minimum porosity can be provided to trap
10 particles therein, such as bound amyloid-beta particles or other bound pathogenic substances. Alternatively, curcumin agent is compounded with catheter material such as silicone or is mechanically entrapped by a substrate such as one disclosed in U.S. Pub. No. 2006/0004317 by Mauge et al. entitled "Hydrocephalus Shunt" which is incorporated herein by reference. Some or
15 all of the length of the catheter can be "doped" with curcumin agent so that it elutes directly into cerebrospinal fluid.

[00030] In constructions where catheter 92 does not define another lumen to return curcumin-exposed cerebrospinal fluid to a sub-dural location, the exposed cerebrospinal fluid is returned to another location within the patient by a catheter 94, such as to the peritoneal cavity. Samples of cerebrospinal fluid, before and/or after exposure to a curcumin agent, can be
20 accomplished through port 96. Alternatively, bound pathogenic substances can be periodically withdrawn from the patient's cerebrospinal fluid and tested or discarded safely.

[00031] The term "curcumin agent" as used herein includes "curcumin", a "curcumin hybrid", and/or a "curcumin analog" as defined below and in a priority application entitled "Methylene Blue-Curcumin Analog for the Treatment of Alzheimer's Disease", U.S. Application
25 No. 12/359,713 filed January 26, 2009 which is incorporated herein by reference in its entirety. Commercial curcumin typically includes three major components: curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%), which are often referred to as "curcuminoids." As used herein, the term "curcumin" includes any one or more of these three major components of commercial curcumin, and any active derivative of these agents. This
30 includes natural and synthetic derivatives of curcumin and curcuminoids, and includes any

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combination of more than one curcumenoid or derivative of curcumin. Derivatives of curcumin and curcumenoids include those derivatives disclosed in U.S. Patent Application Publication 20020019382, which is herein specifically incorporated by reference.

[00032] Modifications of curcumin and its functional fragments that either enhance or do not greatly affect the ability to treat Alzheimer's disease are also included within the term "curcumin." Such modifications include, for example, additions, deletions or replacements of one or more functional groups. These modifications will either enhance or not significantly alter the structure, conformation or functional activity of curcumin or a functional fragment thereof. Additionally, curcumin or its functional fragments can be modified by the addition of epitope tags or other sequences that aid in its purification and which do not greatly affect its activity. As used herein, the term "functional fragment," in connection with an curcumin, is intended to mean any portion of curcumin that maintains its to inhibit oxidation, or to prevent amyloid-beta oligomer formation. If desired, a functional fragment can include regions of the curcumin with activities that beneficially cooperate with the ability to inhibit oxidation or oligomer formation.

[00033] Curcumin is soluble in ethanol, alkalis, ketones, acetic acid and chloroform. It is insoluble in water. Curcumin is therefore lipophilic, and generally readily associates with lipids. In certain embodiments, curcumin can also be formulated as a metal chelate.

[00034] Also in accordance with the present invention, publicly known analogs of curcumin may be used. As used herein, "curcumin analogs" are those compounds which due to their structural similarity to curcumin, exhibit anti-proliferative or pro-apoptotic effects on cancer cells similar to that of curcumin. Curcumin analogs which may have anti-cancer effects similar to curcumin include Ar-tumeronc, methylcurcumin, demethoxy curcumin, bisdemethoxycurcumin, sodium curcumin, dibenzoylmethane, acetylcurcumin, feruloyl methane, tetrahydrocurcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (curcumin1), 1,7-bis(piperonyl)-1,6-heptadiene-3,5-dione(piperonyl curcumin)1,7-bis(2-hydroxy naphthyl)-1,6-heptadiene-2,5-dione(2-hydroxyl naphthyl curcumin), 1,1-bis(phenyl)-1,3,8,10-undecatetraene-5,7-dione (cinnamyl curcumin) and the like (Araujo and Leon, 2001; Lin et al., 2001; John et al., 2002; see also Ishida et al., 2002). Curcumin analogs may also include isomers of curcumin, such as the (Z,E) and (Z,Z) isomers of curcumin. In a related embodiment,

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curcumin metabolites which have anti-cancer effects similar to curcumin can also be used in the present invention. Known curcumin metabolites include glucoronides of tetrahydrocurcumin and hexahydrocurcumin, and dihydroferulic acid. In certain embodiments, curcumin analogs or metabolites can be formulated as metal chelates, especially copper chelates. Other appropriate derivatives of curcumin, curcumin analogs and curcumin metabolites appropriate for use in the present invention will be apparent to one of skill in the art.

[00035] In some embodiments, the curcumin analogs are those found in US Published patent application US 2005/0181036. In other embodiments, the curcumin analogs are those found in US Published patent application US 2006/0067998. In yet other embodiments, the curcumin analogs are those found in US Published patent application US 2005/0267221.

[00036] In certain aspects, 1,7,-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadi- ene-3,5-dione is the curcumin that may be used in the present invention. Other curcumin analogs (curcuminoids) that may be used include, for example, demethoxycurcumin, bisdemethoxycurcumin, dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, dihydroxytetrahydrocurcumin, Yakuchinone A and Yakuchinone B, and their salts, oxidants, reductants, glycosides and esters thereof. Such analogs are described in U.S. Patent Application 20030147979; and U.S. Pat. No. 5,891,924 both of which are incorporated in their entirety herein by reference.

[00037] Other curcumin analogs (curcuminoids) that may be used according to the present invention include dihydroxycurcumin and NDGA. Further examples of curcumin analogs include but are not limited to (a) ferulic acid, (i.e., 4-hydroxy-3-methoxycinnamic acid; 3,4-methylenedioxy cinnamic acid; and 3,4-dimethoxycinnamic acid); (b) aromatic ketones (i.e., 4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one; zingerone; -4-(3,4-methylenedioxyphenyl)-2-butanone; 4-(p-hydroxyphenyl)-3-buten-2-one; 4-hydroxyvalerophenone; 4-hydroxybenzylactone; 4-hydroxybenzophenone; 1,5-bis(4-dimethylaminophen- yl)-1,4-pentadien-3-one); (c) aromatic diketones (i.e., 6-hydroxydibenzoylmethane) (d) caffeic acid compounds (i.e., 3,4-dihydroxycinnamic acid); (e) cinnamic acid; (f) aromatic carboxylic acids (i.e., 3,4-dihydroxyhydrocinnamic acid; 2-hydroxycinnamic acid; 3-hydroxycinnamic acid and 4-hydroxycinnamic acid); (g) aromatic ketocarboxylic acids (i.e., 4-hydroxyphenylpyruvic acid); and (h) aromatic alcohols (i.e., 4-hydroxyphenethyl alcohol). These analogs and other

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representative analogs that can be used in the present invention are further described in WO9518606 and WO01040188, which are incorporated herein by reference in their entirety.

[00038] Curcumin or analogs thereof may be purified from plants or chemically synthesized using methods well known and used by those of skill in the art. Plant-derived curcumin and/or its analogs can be obtained by extraction from plants including Zingiberaceae Curcuma, such as Curcuma longa (turmeric), Curcuma aromatica (wild turmeric), Curcuma zedoaria (zedoary), Curcuma xanthorrhiza, mango ginger, Indonesian arrowroot, yellow zedoary, black zedoary and galangal. Methods for isolating curcuminoids from turmeric are well known in the art (Janaki and Bose, 1967). Still further, curcumin may be obtained from commercial sources, for example, curcumin can be obtained from Sigma Chemicals Co (St. Louis, Mo.).

[00039] Any conventional method can be used to prepare curcumin and its analogs to be used in the present invention. For example, turmericoleoresin, a food additive, which essentially contains curcumin, can be produced by extracting from a dry product of rhizome of turmeric with ethanol at an elevated temperature, with hot oil and fat or propylene glycol, or with hexane or acetone at from room temperature to a high temperature. Alternatively, those can be produced by the methods disclosed in Japanese Patent Applications 2000-236843, H-11-235192 and H-6-9479, and U.S. Patent Application No. 20030147979, which is incorporated by reference herein in its entirety.

[00040] In certain embodiments, a purified product of at least one curcumin and/or its analog may be delivered to cerebrospinal fluid according to the present invention. Alternatively, a semi-purified or crude product thereof may be used, provided that it does not contain impurities which may not be acceptable as a pharmaceutical or food product.

[00041] There has been limited testing of the potency of curcumin analogs against amyloid-beta. Park, J. Nat. Prod., 65,9, Sept. 2002, reports testing the following curcumin analogs for the ability to provide in vitro protection for PC12 cells against amyloid-beta insult (with reference numbers 31-34 from FIG. 1d of U.S. Appln. 12.359,713 which has been incorporated herein by reference:

4''-(3'''-methoxy-4'''-hydroxyphenyl)-2''-oxo-3''-enebutanyl3-(3'-methoxy-4'hydroxyphenyl) propenoate (31);

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1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (demethoxycurcumin)(32);

1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (bisdemethoxycurcumin), (33); and

1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione (34).

5 [00042] Analysis of the Park data reveals that each of compounds (31)-(34) is a more potent neuroprotectant against amyloid-beta than curcumin, with compounds (31) and (34) being on the order of 5 and 10 fold more potent. Therefore, in preferred embodiments, each of compounds (31)-(34) is used by itself or in combination as the parent compound for the manufacturing and use of a curcumin prodrug. Each of the parent compounds may be obtained
10 by the methods disclosed in Park.

[00043] In other embodiments, the curcumin is combined with a second lipophilic therapeutic agent, preferably another polyphenol such as resveratrol, to form a "curcumin hybrid" which is delivered to cerebrospinal fluid according to the present invention. In some embodiments, the curcumin is provided in a formulation with another compound selected from
15 the group consisting of ginkgo biloba extract, resveratrol, hispidin, genistein, ellagic acid, 1,25 dihydroxyvitamin D3, the green tea catechin EGCG, and docosahexaenoic acid (DHA).

[00044] There are a number of curcumin hybrids as well as analogs described in U.S. Appln. No. 12/359,713, which has been incorporated herein by reference, to be delivered to cerebrospinal fluid according to the present invention. Figures 2-16 of U.S. Appln. No.
20 12/359,713 disclose various curcumin derivatives that are hybrids of curcumin and various other natural polyphenols. Each of these derivatives is a triphenolic compound, wherein the intermediate diketone structure of curcumin is replaced with a phenolic group. The resulting compound retains the spacing between the two phenols of curcumin, and also possesses the biphenolic spacing of the additional polyphenol. FIG. 2 of U.S. Appln. No. 12/359,713 discloses
25 the structures of curcumin, resveratrol, and two curcumin-resveratrol hybrids. Each of the hybrids retains the interphenolic spacing of each of curcumin and reveratrol. FIG. 3 of U.S. Appln. No. 12/359,713 discloses a method of making the curcumin-resveratrol I hybrid. FIG. 4 of U.S. Appln. No. 12/359,713 discloses a method of making the curcumin-resveratrol II hybrid.

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FIG. 5 of U.S. Appln. No. 12/359,713 discloses a method of making a curcumin-resveratrol hybrid having three hydroxyl groups in each of the central phenolic group and lateral phenolic groups. FIG. 6 of U.S. Appln. No. 12/359,713 discloses curcumin, resveratrol and a hybrid thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a dihydroxyl central phenolic group. FIG. 7 of U.S. Appln. No. 12/359,713 discloses a method of making the curcumin-resveratrol hybrid of FIG. 6. FIG. 8 of U.S. Appln. No. 12/359, 713 is similar to the hybrid of FIG. 6, but wherein the methoxy groups of the base curcumin molecule are retained. FIG. 9 of U.S. Appln. No. 12/359,713 discloses curcumin, oxyresveratrol and a hybrid thereof, wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a trihydroxyl central phenolic group. FIG. 10 of U.S. Appln. No. 12/359,713 discloses curcumin, piceatannol and a hybrid thereof, wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a trihydroxyl central phenolic group. FIG. 11 of U.S. Appln. No. 12/359,713 discloses a method of making a curcumin-resveratrol hybrid, wherein all of the hydroxyls/phenolics of the natural compounds are represented in the hybrid, providing trihydroxyl lateral phenolic groups and a dihydroxyl central phenolic group.

[00045] FIG.12 of U.S. Appln. No. 12/359,713, incorporated herein by reference, discloses curcumin, BDMC, resveratrol and curcumin hybrids thereof, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing hydroxyl demethoxy lateral phenolic groups and a hydroxy or dihydroxyl central phenolic group. FIG. 13 of U.S. Appln. No. 12/359,713 provides a method of making the compound of FIG. 12 that has hydroxyl demethoxy lateral phenolic groups and a hydroxy central phenolic group. The curcumin analog molecule shown in FIG. 13 is 1-hydroxyl 3,5-bis (4'-hydroxyl styryl) benzene. Through simple deletion of a methoxy group in one of the reactants, 3,5-bis (4'-hydroxyl styryl) benzene can be made via method substantially similar to that shown in FIG. 13. FIG. 14 of U.S. Appln. No. 12/359,713 provides a method of making the compound of FIG. 12 that has hydroxyl demethoxy lateral phenolic groups and a dihydroxy central phenolic group. The curcumin analog molecule shown in FIG. 14 is 1,3-dihydroxyl 4,6-bis (4'-hydroxyl styryl) benzene.

[00046] Figure 15 of U.S. Appln. No. 12/359,713 discloses curcumin, piccatannol and a hybrid thereof, wherein most of the hydroxyls of the natural compounds are represented in the hybrid, providing dihydroxyls in the end phenolic groups and a single hydroxyl in the central phenolic group in the positions common with the two natural compounds. Kim, Ann N Y Acad Sci., 2007 Jan;1095:473-82 reports that piccatannol treatment attenuates the intracellular accumulation of ROS induced by treatment of PC12 cells with A β , and inhibited A β -induced apoptotic features including internucleosomal DNA fragmentation, nucleus condensation, cleavage of poly(ADP-ribose) polymerase (PARP), and activation of caspase-3. The curcumin-piceatannol analog molecule shown in FIG. 15 is 1-hydroxyl 3,5-bis (3', 4'-dihydroxyl styryl) benzene. Through simple deletion of a methoxy group in one of the reactants, 3,5-bis (3', 4'-dihydroxyl styryl) benzene, can be made via method substantially similar to that shown in FIG. 15. FIG. 16 of U.S. Appln. No. 12/359,713 provides a method of making the compound of FIG. 15.

[00047] In some embodiments, a curcumin analog is utilized comprising at least one structure selected from the group consisting of:

- a) 1-hydroxyl 3,5-bis (4'-hydroxyl styryl) benzene,
- b) 1,3-dihydroxyl 4,6-bis (4'-hydroxyl styryl) benzene,
- c) 1-hydroxyl 3,5-bis (3', 4'-dihydroxyl styryl) benzene, and
- d) 3,5-bis (3', 4'-dihydroxyl styryl) benzene.

In some embodiments, a curcumin analog is utilized comprising 1-hydroxyl 3,5-bis (4'-hydroxyl styryl) benzene. In some embodiments, there is provided a curcumin analog comprising 3,5-bis (4'-hydroxyl styryl) benzene. In some embodiments, there is provided a curcumin analog comprising 1,3-dihydroxyl 4,6-bis (4'-hydroxyl styryl) benzene. In some embodiments, there is provided a curcumin analog comprising 1-hydroxyl 3,5-bis (3', 4'-dihydroxyl styryl) benzene. In some embodiments, there is provided a curcumin analog comprising 3,5-bis (3', 4'-dihydroxyl styryl) benzene.

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[00048] Further curcumin hybrids delivered to cerebrospinal fluid according to the present invention are disclosed in Figures 17-22 of U.S. Appln. No. 12/359,713 and are incorporated herein by reference. FIG. 17 of U.S. Appln. No. 12/359,713 discloses the structures of curcumin, 3,3',4' fisetin and a curcumin- 3,3',4' fisetin hybrid, wherein all of the hydroxyls of the curcumin and 3,3',4' fisetin compounds are represented in the hybrid, providing dihydroxyls in the end phenolic groups and a hydroxyl in the place of each double bond. Maher, Free Radic Res. 2006 Oct;40(10):1105-11 reports that fisetins in general and 3,3',4' fisetin in particular have potent (low micromolar) neurotrophic properties. FIG. 18 of U.S. Appln. No. 12/359,713 discloses a method of making the curcumin-3,3',4' fisetin hybrid of FIG. 17. FIG. 19 of U.S. Appln. No. 12/359,713 discloses the structures of curcumin, honokiol and a curcumin- honokiol hybrid, wherein all of the hydroxyls of the curcumin and honokiol compounds are represented in the hybrid, providing a single hydroxyl in the end phenolic groups and a hydroxyl in the place of each double bond. Fukuyama, Bioorg Med Chem Lett. 2002 Apr 22;12(8):1163-6 reports that honokiol has potent neurotrophic properties. FIG. 20 of U.S. Appln. No. 12/359,713 discloses a method of making the curcumin- honokiol hybrid of FIG. 19. FIG. 21 of U.S. Appln. No. 12/359,713 discloses a method of making a FIG. 13 - honokiol hybrid, wherein all of the hydroxyls of the natural compounds are represented in the hybrid, providing single hydroxyl in the end phenolic groups in the positions common with the two natural compounds, a hydroxyl in the central phenolic group, and a hydroxyl in the place of each curcumin double bond. FIG. 22 of U.S. Appln. No. 12/359,713 discloses a method of making a FIG. 15 - 3,3',4' fisetin hybrid, wherein all of the phenolics of the natural compounds are represented in the hybrid, providing single hydroxyl in the end phenolic groups and a hydroxy central phenolic group in the positions common with the two natural compounds, and an additional hydroxyl in the place of each curcumin double bond.

[00049] Another curcumin hybrid delivered to cerebrospinal fluid according to the present invention includes methylene blue as disclosed in U.S. Appln. No. 12/359,713 and incorporated herein by reference. As noted in U.S. Appln. No. 12/359,713, the seven-carbon hydrophobic medial section of curcumin (or BDMC) has the same length as the nonpolar tricyclic medial section of methylene blue. Moreover, the seven-carbon hydrophobic medial section of curcumin (or BDMC) provides resonance through spaced double bonds in a manner likely to be

functionally similar to the double bonds of the nonpolar tricyclic section of methylene blue. Accordingly, it is believed that the pair of lateral hydroxyphenyl groups of curcumin (or BDMC) can be added onto methylene blue in a manner that preserves both their spatial relationship (and therefore their amyloid binding ability) and their interaction with the medial double bonds of curcumin. The result thereof is a molecule (50) having many of the desirable qualities of both curcumin and methylene blue. This molecule (50) is shown in FIG. 29 U.S. Appl. No. 12/359,713 and is named 2,6-bis (4', 4'' dihydroxyphenyl), 3,7-bis (dimethylamino)-phenazathionium chloride. Therefore, in another embodiment of the present invention, there is provided a hybrid of curcumin (or BDMC) and methylene blue which is delivered to cerebrospinal fluid according to the present invention. This hybrid of BDMC and methylene blue is shown as molecule (50) in FIG. 29 of U.S. Appl. No. 12/359,713.

[00050] Thus, while there have been shown, described, and pointed out fundamental novel features of the invention as applied to preferred embodiments thereof, it will be understood that various omissions, substitutions, and changes in the form and details of the devices illustrated, and in their operation, may be made by those skilled in the art without departing from the spirit and scope of the invention. For example, it is expressly intended that all combinations of those elements and/or steps that perform substantially the same function, in substantially the same way, to achieve the same results be within the scope of the invention. Substitutions of elements from one described embodiment to another are also fully intended and contemplated. It is also to be understood that the drawings are not necessarily drawn to scale, but that they are merely conceptual in nature. It is the intention, therefore, to be limited only as indicated by the scope of the claims appended hereto.

[00051] Every issued patent, pending patent application, publication, journal article, book or any other reference cited herein is each incorporated by reference in their entirety.

Claims

What is claimed is:

1. A method for reducing or preventing a human brain disorder relating to the presence of a pathogenic substance in cerebrospinal fluid, comprising:
 - selecting a human for treatment as a patient;
 - placing a proximal end of a first catheter, having at least a first lumen, in a first sub-dural location within the brain of the patient to establish open communication between the first lumen and cerebrospinal fluid of the patient; and
 - delivering to the cerebrospinal fluid for an extended period of time a curcumin agent selected from at least one of curcumin, a curcumin hybrid and a curcumin analog to interact with the pathogenic substance to attenuate its effect on the brain.
2. The method of claim 1 wherein the patient has been diagnosed as having a brain disorder.
3. The method of claim 1 wherein the patient has been diagnosed as having Alzheimer's disease.
4. The method of claim 1 wherein the proximal end of the catheter is placed within a ventricle of the brain as the first sub-dural location.
5. The method of claim 1 wherein cerebrospinal fluid intermixed with the curcumin agent is returned directly to the first sub-dural location.
6. The method of claim 1 wherein cerebrospinal fluid intermixed with the curcumin agent is returned directly to another sub-dural location within the brain of the patient.
7. The method of claim 1 wherein the curcumin agent achieves a brain tissue concentration of at least 0.1 μM .
8. The method of claim 1 wherein the curcumin agent achieves a brain tissue concentration of at least 1 μM .
9. The method of claim 1 wherein the curcumin agent achieves a brain tissue concentration of at least 5 μM .
10. The method of claim 1 wherein the curcumin agent achieves a brain tissue concentration of at least 20 μM .
11. The method of claim 1 wherein the curcumin agent is released from a reservoir connected to the first catheter.

12. The method of claim 11 wherein a proximal catheter connected to the reservoir transports cerebrospinal fluid intermixed with the curcumin agent to another location within the patient.
13. The method of claim 11 wherein the reservoir includes a removable canister carrying curcumin agent.
14. The method of claim 1 wherein at least some of the curcumin agent is released from a coating carried within at least a portion of the first catheter.
15. The method of claim 1 further including sampling cerebrospinal fluid at a sub-dural location that is different than the first sub-dural location and measuring the concentration of the curcumin agent in the cerebrospinal fluid.
16. A method for reducing or preventing a human brain disorder relating to the presence of a pathogenic substance in cerebrospinal fluid, comprising:
 - selecting a human for treatment as a patient;
 - placing a proximal end of a first catheter, having at least a first lumen, in a first sub-dural location within the brain of the patient to establish open communication between the first lumen and cerebrospinal fluid;
 - withdrawing cerebrospinal fluid through the first lumen and exposing it to a curcumin agent including at least one of curcumin, a curcumin hybrid and a curcumin analog to interact with the pathogenic substance to attenuate its effect on the brain; and
 - returning the exposed cerebrospinal fluid to the patient, wherein the curcumin agent achieves a brain tissue concentration of at least 0.1 μ M.
17. The method of claim 16 wherein the exposed cerebrospinal fluid is returned to the patient through a second lumen of the first catheter.
18. The method of claim 16 wherein the exposed cerebrospinal fluid is returned to the patient through a lumen of a second catheter.
19. The method of claim 16 further including sampling cerebrospinal fluid at a sub-dural location that is different than the first sub-dural location and measuring the concentration of the curcumin agent in the cerebrospinal fluid to estimate its brain tissue concentration.
20. A method for reducing a human brain dementia relating to the presence of a pathogenic substance in cerebrospinal fluid, comprising:
 - selecting a human for treatment as a patient that has been diagnosed with dementia;

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placing a proximal end of a first catheter, having at least a first lumen, in a first sub-meningeal location within the brain of the patient to establish open communication between the first lumen and cerebrospinal fluid of the patient; and

delivering to the cerebrospinal fluid for an extended period of time a curcumin agent selected from at least one of curcumin, a curcumin hybrid and a curcumin analog to interact with the pathogenic substance to attenuate its effect on the brain, wherein the curcumin agent is released from a reservoir connected to the first catheter and achieves a brain tissue concentration of at least 1 μM .

21. The method of claim 20 further including sampling cerebrospinal fluid at a sub-dural location that is different than the first sub-dural location and measuring the concentration of the curcumin agent in the cerebrospinal fluid to estimate its brain tissue concentration.

Abstract

A method for reducing or preventing a human brain disorder relating to the presence of a pathogenic substance in cerebrospinal fluid by selecting a human for treatment as a patient and placing a proximal end of a first catheter, having at least a first lumen, in a first sub-dural location within the brain of the patient to establish open communication between the first lumen and cerebrospinal fluid of the patient. For an extended period of time, a curcumin agent selected from at least one of curcumin, a curcumin hybrid and a curcumin analog is delivered to the cerebrospinal fluid to interact with the pathogenic substance to attenuate its effect on the brain.

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.53) ☒ Declaration Submitted with Initial Filing. ☐ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.18(e)) required)	Attorney Docket Number	COD5222USCIP1
	First Named Inventor	Thomas M. DiMauro
	COMPLETE IF KNOWN	
	Application Number	Not Assigned
	Filing Date	Not Assigned
	Group Art Unit	Not Assigned
	Examiner Name	Not Assigned

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Shunt Delivery of Curcumin
(Title of the Invention)

the specification of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) [] as United States Application Number or PCT International Application Number [] and was amended on (MM/DD/YYYY) [] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

AUTHORIZATION TO PERMIT ACCESS TO APPLICATION BY PARTICIPATING OFFICES

The undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, or other intellectual property office in which a foreign application claiming priority to the above-identified application is filed to have access to the application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the application as filed with respect to: 1) the above-identified application, 2) any foreign application to which the above-identified application claims priority under 35 USC 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified US application, and 3) any U.S. application from which benefit is sought in the above-identified application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

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Inventor's Signature <i>Thomas M DiMauro</i>		Date 1-27-10
Inventor Two: Alan Dextradeur		
Mailing Address 15 Lyons Street, Franklin, MA 02038		Citizenship US
Inventor's Signature		Date
Inventor Three: Sean Lillienfeld		
Mailing Address 12 Terrapin Lane, Sharon, MA 02067		Citizenship SA
Inventor's Signature		Date
Inventor Four: Krishna Venugopalan		
Mailing Address 14 Old Cart Path, Holliston, MA 01746		Citizenship US
Inventor's Signature		Date

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) ☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.16(e)) required)	Attorney Docket Number	COD5222USCIP1
	First Named Inventor	Thomas M. DiMauro
	COMPLETE IF KNOWN	
	Application Number	Not Assigned
	Filing Date	Not Assigned
	Group Art Unit	Not Assigned
	Examiner Name	Not Assigned

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Shunt Delivery of Curcumin
(Title of the Invention)

the specification of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) [] as United States Application Number or PCT International Application Number [] and was amended on (MM/DD/YYYY) [] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

AUTHORIZATION TO PERMIT ACCESS TO APPLICATION BY PARTICIPATING OFFICES

The undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, or other intellectual property office in which a foreign application claiming priority to the above-identified application is filed to have access to the application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the application-as-filed with respect to: 1) the above-identified application, 2) any foreign application to which the above-identified application claims priority under 35 USC 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified US application, and 3) any U.S. application from which benefit is sought in the above-identified application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

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I hereby appoint:		Place Customer Number Bar Code Label Here
☒	Practitioners at Customer Number <u>000027777</u>	
AND		
☐	Practitioner(s) named below: Name _____ Registration Number _____	
as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.		
Address all telephone calls to Eugene L. Szczecina, Jr. at telephone number (732) 524-1479.		
Direct all correspondence to:	☒ Customer Number or Bar Code Label <u>000027777</u>	
I hereby declare that all statements made herein of my own knowledge are true 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 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.		
FULL NAME OF INVENTOR(S)		
Inventor One: Thomas M. DiMauro		
Mailing Address	3 Fitzgerald Lane, Southborough, MA 01772	Citizenship US
Inventor's Signature		Date
Inventor Two: Alan Dextradeur		
Mailing Address	15 Lyons, Street, Franklin, MA 02038	Citizenship US
Inventor's Signature	<i>Alan Dextradeur</i>	Date 1-14-2010
Inventor Three: Sean Lillienfeld		
Mailing Address	12 Terrapin Lane, Sharon, MA 02087	Citizenship SA
Inventor's Signature		Date
Inventor Four: Krishna Venugopalan		
Mailing Address	14 Old Cart Path, Holliston, MA 01746	Citizenship US
Inventor's Signature		Date

35

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) ☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.16(e)) required)	Attorney Docket Number	COD5222USCIP1
	First Named Inventor	Thomas M. DiMauro
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	Application Number	Not Assigned
	Filing Date	Not Assigned
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Shunt Delivery of Curcumin
(Title of the invention)

the specification of which

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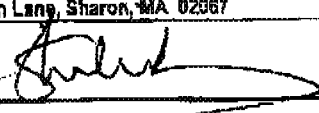
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☒	Practitioners at Customer Number <u>000027777</u>	
AND		
☐	Practitioner(s) named below:	
	Name	Registration Number
as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.		
Address all telephone calls to Eugene L. Szczecina, Jr. at telephone number (732) 524-1479.		
Direct all correspondence to:		
	Customer Number	
☒	or Bar Code Label	<u>000027777</u>
I hereby declare that all statements made herein of my own knowledge are true 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 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.		
FULL NAME OF INVENTOR(S)		
Inventor One: Thomas M. DiMauro		
Mailing Address	3 Fitzgerald Lane, Southborough, MA 01772	Citizenship US
Inventor's Signature		Date
Inventor Two: Alan Dextradeur		
Mailing Address	15 Lyons Street, Franklin, MA 02038	Citizenship US
Inventor's Signature		Date
Inventor Three: Sean Lillienfeld		
Mailing Address	12 Terrapin Lane, Sharon, MA 02067	Citizenship MA US
Inventor's Signature		Date 1/13/10
Inventor Four: Krishna Venugopalan		
Mailing Address	14 Old Cart Path, Holliston, MA 01748	Citizenship US
Inventor's Signature		Date

37

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) ☒ Declaration Submitted with Initial Filing ☐ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.16(e)) required) OR	Attorney Docket Number	COD5222USCIP1
	First Named Inventor	Thomas M. DiMeuro
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	Application Number	Not Assigned
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	Examiner Name	Not Assigned

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Shunt Delivery of Curcumin
(Title of the Invention)

the specification of which

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I hereby appoint:		Place Customer Number Bar Code Label Here
☒ Practitioner at Customer Number 000027777 →		
AND		
☐ Practitioner(s) named below: <u>Name</u> <u>Registration Number</u>		
as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.		
Address all telephone calls to Eugene L. Szczecina, Jr. at telephone number (732) 524-1479.		
Direct all correspondence to: ☒ Customer Number 000027777		
I hereby declare that all statements made herein of my own knowledge are true 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 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.		
FULL NAME OF INVENTOR(S)		
Inventor One: Thomas M. DiMauro		
Mailing Address 3 Fitzgerald Lane, Southborough, MA 01772	Citizenship US	
Inventor's Signature	Date	
Inventor Two: Alan Dextradeur		
Mailing Address 15 Lyons, Street, Franklin, MA 02036	Citizenship US	
Inventor's Signature	Date	
Inventor Three: Sean Lillienfeld		
Mailing Address 12 Terrapin Lane, Sharon, MA 02067	Citizenship SA	
Inventor's Signature	Date	
Inventor Four: Ramekrahna Venugopalan		
Mailing Address 15 Old Cart Path, Holliston, MA 01746	Citizenship US	
Inventor's Signature <i>R. Venugopalan</i>	Date 14 JAN 10	

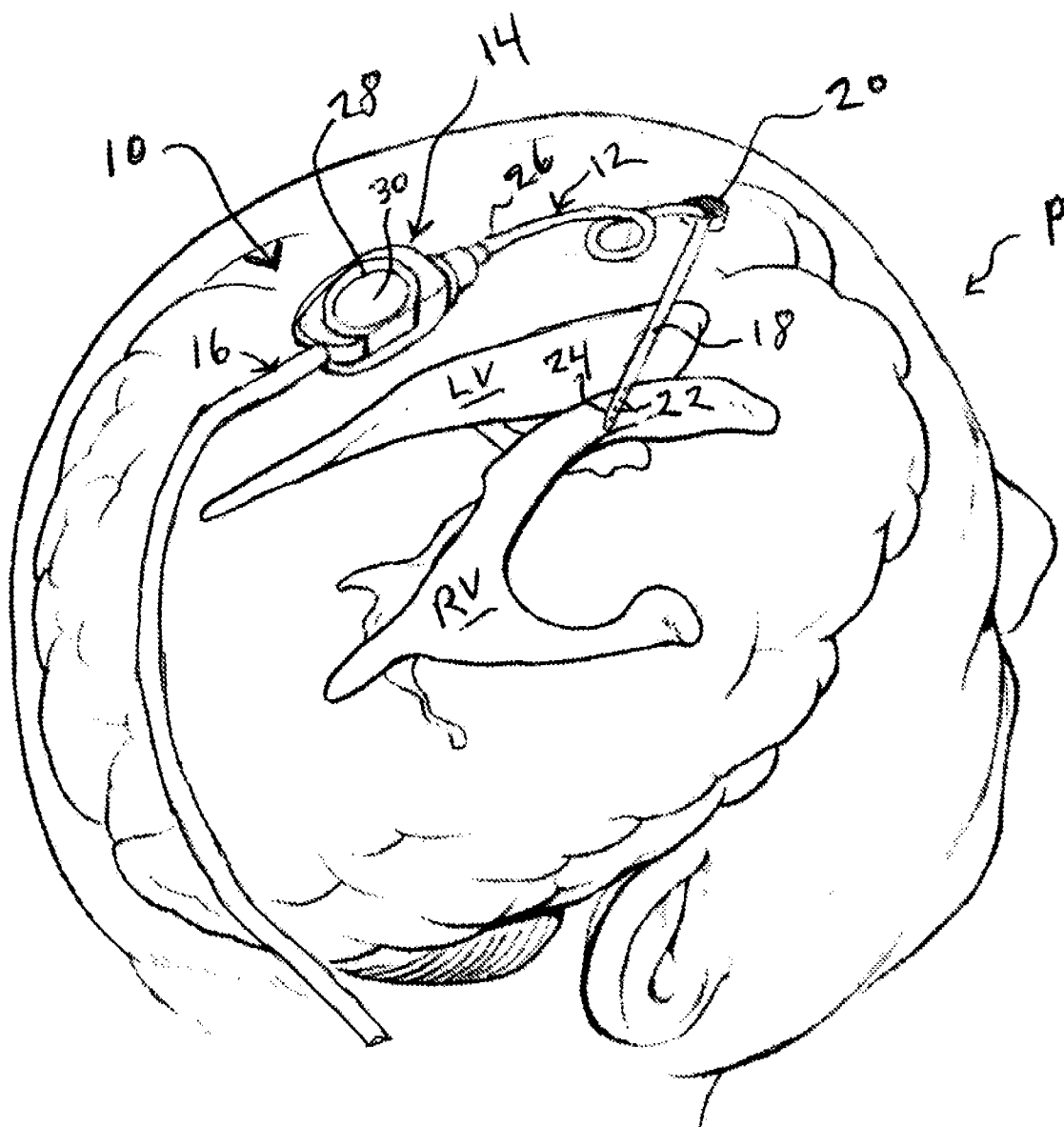


FIG. 1 A

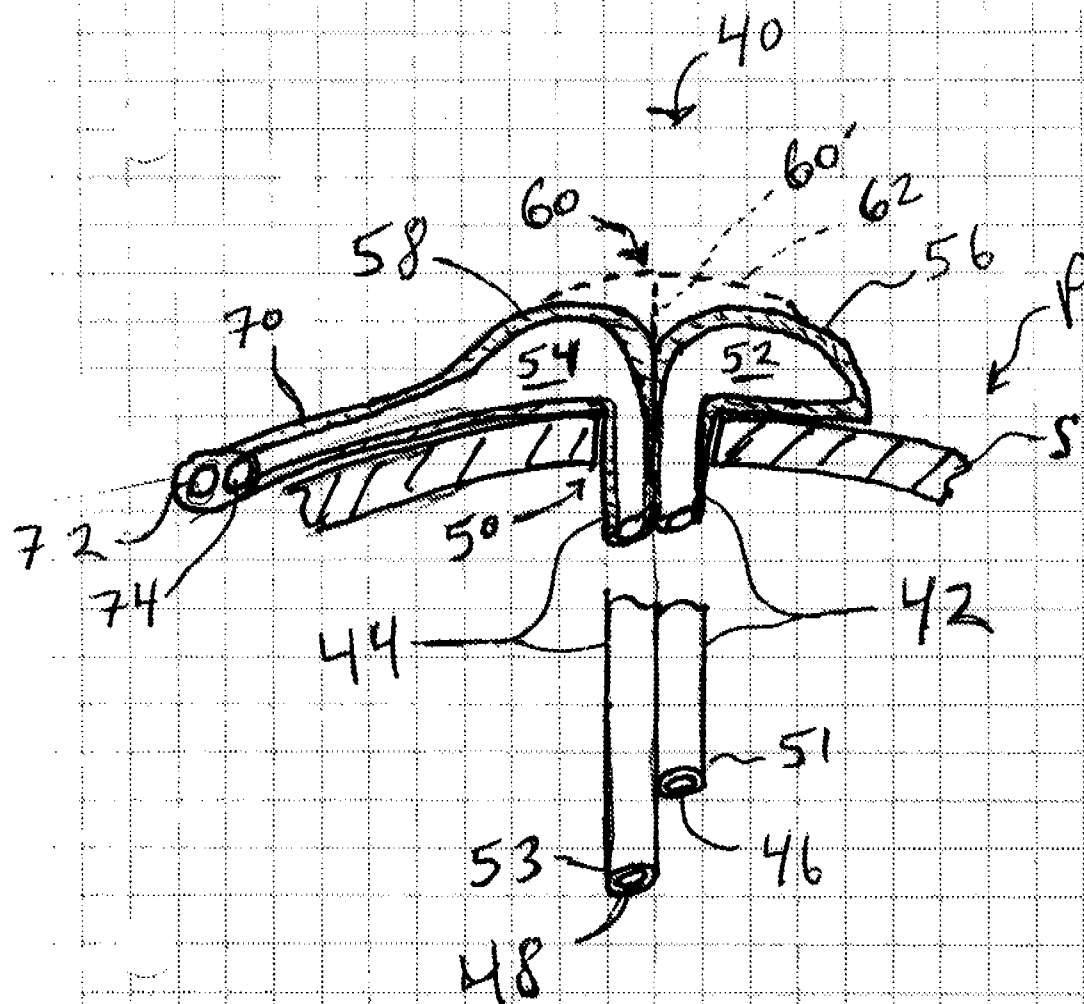


FIG. 1B

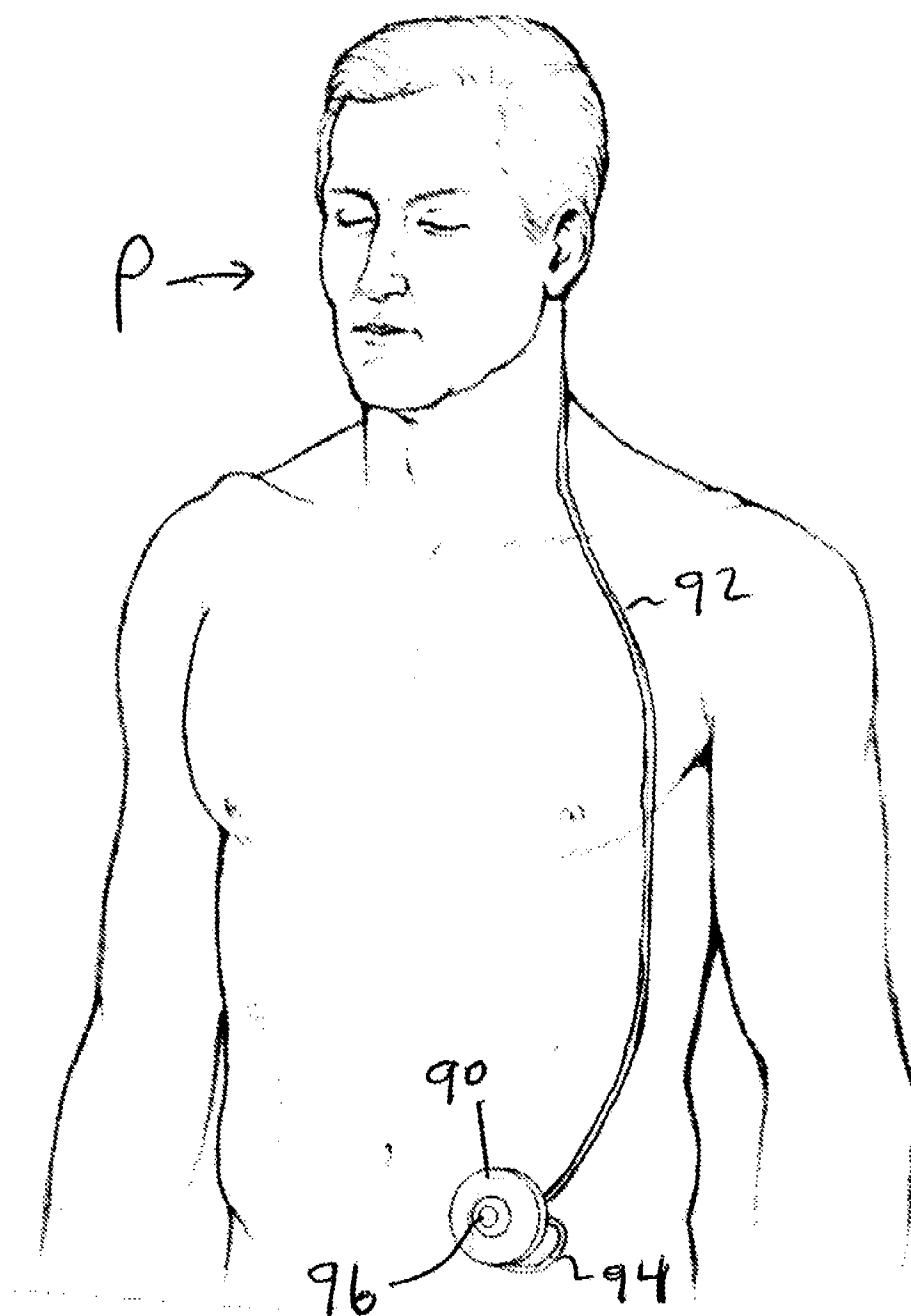


FIG. 1C

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	COD5222USCIP1
		Application Number	
Title of Invention	Shunt Delivery of Curcumin		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1					Remove			
Applicant Authority		☒ Inventor		☐ Legal Representative under 35 U.S.C. 117		☐ Party of Interest under 35 U.S.C. 118		
Prefix	Given Name	Middle Name		Family Name		Suffix		
	Thomas	M		DiMauro				
Residence Information (Select One)							☒ US Residency ☐ Non US Residency ☐ Active US Military Service	
City	Southborough		State/Province	MA	Country of Residence i	US		
Citizenship under 37 CFR 1.41(b) i			US					
Mailing Address of Applicant:								
Address 1		3 Fitzgerald Lane						
Address 2								
City	Southborough			State/Province	MA			
Postal Code		01772		Country i	US			
Applicant 2								Remove
Applicant Authority		☒ Inventor		☐ Legal Representative under 35 U.S.C. 117		☐ Party of Interest under 35 U.S.C. 118		
Prefix	Given Name	Middle Name		Family Name		Suffix		
	Alan			Dextrateur				
Residence Information (Select One)							☒ US Residency ☐ Non US Residency ☐ Active US Military Service	
City	Franklin		State/Province	MA	Country of Residence i	US		
Citizenship under 37 CFR 1.41(b) i			US					
Mailing Address of Applicant:								
Address 1		15 Lyons, Street						
Address 2								
City	Franklin			State/Province	MA			
Postal Code		02038		Country i	US			
Applicant 3								Remove
Applicant Authority		☒ Inventor		☐ Legal Representative under 35 U.S.C. 117		☐ Party of Interest under 35 U.S.C. 118		
Prefix	Given Name	Middle Name		Family Name		Suffix		
	Sean			Lilienfeld				
Residence Information (Select One)							☒ US Residency ☐ Non US Residency ☐ Active US Military Service	
City	Sharon		State/Province	MA	Country of Residence i	US		

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PTO/SB/14 (08-05)

Approved for use through 07/31/2006. OMB 0851-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	COD5222USCIP1
		Application Number	
Title of Invention	Shunt Delivery of Curcumin		

Citizenship under 37 CFR 1.41(b) i		US	
Mailing Address of Applicant:			
Address 1	12 Terrapin Lane		
Address 2			
City	Sharon,	State/Province	MA
Postal Code	02067	Country ⁱ	
Applicant 4			Remove
Applicant Authority		☒ Inventor ☐ Legal Representative under 35 U.S.C. 117 ☐ Party of Interest under 35 U.S.C. 118	
Prefix	Given Name	Middle Name	Family Name Suffix
	Krishna		Venugopalan
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service			
City	Holliston	State/Province	MA Country of Residence ⁱ US
Citizenship under 37 CFR 1.41(b) i		US	
Mailing Address of Applicant:			
Address 1	14 Old Cart Path,		
Address 2			
City	Holliston,	State/Province	MA
Postal Code	01746	Country ⁱ	US
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.			Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence Information of this application.	
Customer Number	27777
Email Address	JNJUSPATENT@CORUS.JNJ.COM Add Email Remove Email

Application Information:

Title of the Invention	Shunt Delivery of Curcumin		
Attorney Docket Number	COD5222USCIP1	Small Entity Status Claimed ☐	
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	3	Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	COD5222USCIP1
		Application Number	
Title of Invention	Shunt Delivery of Curcumin		

Publication Information:	
☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not been and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.			
Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ US Representative (37 CFR 11.9)
Customer Number	27777		

Domestic Priority Information:

This section allows for the applicant to claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c). Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.			
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation in part of	12/359713	2009-01-26
Additional Domestic Priority Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).			
Remove			
Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			☒ Yes ☐ No
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.	
Assignee 1	Remove
If the Assignee is an Organization check here. ☒	

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number		COD5222USCIP1	
		Application Number			
Title of Invention		Shunt Delivery of Curcumin			
Organization Name		Codman & Shurtleff, Inc.			
Mailing Address Information:					
Address 1		325 Paramount Drive			
Address 2					
City		Raynham		State/Province	MA
Country	US	Postal Code		02767	
Phone Number				Fax Number	
Email Address					
Additional Assignee Data may be generated within this form by selecting the Add button.					
Add					

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Eugene L. Szczecina, Jr./		Date (YYYY-MM-DD)	2010-01-29	
First Name	Eugene L.	Last Name	Szczecina	Registration Number	35029

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

REIVINDICACIONES:

1. Un método para reducir o prevenir un trastorno del cerebro humano relacionado con la presencia de una sustancia patógena en el líquido cefalorraquídeo;

5 el método comprende:

seleccionar a un ser humano para tratarlo como paciente;

colocar un extremo proximal de un primer catéter, que tiene por lo menos un primer lumen, en un primer lugar subdural en el cerebro del paciente para establecer una comunicación abierta entre el primer lumen y el líquido cefalorraquídeo del paciente; y

10 por un periodo de tiempo prolongado, administrar un agente de curcumina seleccionado de por lo menos uno, entre un híbrido de curcumina y un análogo de curcumina, al líquido cefalorraquídeo para que interactúe con la sustancia patógena para atenuar su efecto en el cerebro.

2. El método de conformidad con la reivindicación 1, caracterizado además
15 porque al paciente se le ha diagnosticado un desorden cerebral.

3. El método de conformidad con la reivindicación 1, caracterizado además porque al paciente se le ha diagnosticado la enfermedad de Alzheimer.

4. El método de conformidad con la reivindicación 1, caracterizado además
20 porque el extremo proximal del catéter se coloca en un ventrículo del cerebro como el primer lugar subdural.

5. El método de conformidad con la reivindicación 1, caracterizado además porque el líquido cefalorraquídeo mezclado con el agente de curcumina se devuelve directamente al primer lugar subdural.

6. El método de conformidad con la reivindicación 1, caracterizado además porque el líquido cefalorraquídeo mezclado con el agente de curcumina se devuelve directamente a otro lugar subdural en el cerebro del paciente.
7. El método de conformidad con la reivindicación 1, caracterizado además porque el agente de curcumina alcanza una concentración de tejido cerebral de por lo menos 0,1 μM .
8. El método de conformidad con la reivindicación 1, caracterizado además porque el agente de curcumina alcanza una concentración de tejido cerebral de por lo menos 1 μM .
9. El método de conformidad con la reivindicación 1, caracterizado además porque el agente de curcumina alcanza una concentración de tejido cerebral de por lo menos 5 μM .
10. El método de conformidad con la reivindicación 1, caracterizado además porque el agente de curcumina alcanza una concentración de tejido cerebral de por lo menos 20 μM .
11. El método de conformidad con la reivindicación 1, caracterizado además porque el agente de curcumina se libera desde un receptáculo conectado al primer catéter.
12. El método de conformidad con la reivindicación 11, caracterizado además porque un catéter proximal conectado al receptáculo transporta el líquido cefalorraquídeo mezclado con el agente de curcumina a otro lugar dentro del paciente.
13. El método de conformidad con la reivindicación 11, caracterizado además porque el receptáculo incluye un frasco removible que lleva el agente de curcumina.
14. El método de conformidad con la reivindicación 1, caracterizado además porque por lo menos un poco del agente de curcumina se libera desde un revestimiento que se lleva en por lo menos una porción del primer catéter.

15. El método de conformidad con la reivindicación 1 que incluye, además, tomar muestras de líquido cefalorraquídeo en un lugar subdural que es distinto del primer lugar subdural y medir la concentración del agente de curcumina en el líquido cefalorraquídeo.

16. Un método para reducir o prevenir un trastorno del cerebro humano
5 relacionado con la presencia de una sustancia patógena en el líquido cefalorraquídeo; el método comprende:

seleccionar a un ser humano para tratarlo como paciente;

colocar un extremo proximal de un primer catéter, que tiene por lo menos un
primer lumen, en un primer lugar subdural en el cerebro del paciente para establecer
10 una comunicación abierta entre el primer lumen y el líquido cefalorraquídeo;

extraer líquido cefalorraquídeo por el primer lumen y exponerlo a un agente de curcumina que incluye por lo menos uno, entre curcumina, un híbrido de curcumina y un análogo de curcumina, para que interactúe con la sustancia patógena para atenuar su efecto en el cerebro; y

15 devolver el líquido cefalorraquídeo expuesto al paciente, caracterizado además porque el agente de curcumina alcanza una concentración de tejido cerebral de por lo menos 0,1 μM .

17. El método de conformidad con la reivindicación 16, caracterizado además porque el líquido cefalorraquídeo expuesto se devuelve al paciente por un segundo
20 lumen del primer catéter.

18. El método de conformidad con la reivindicación 16, caracterizado además porque el líquido cefalorraquídeo expuesto se devuelve al paciente por el lumen de un segundo catéter.

19. El método de conformidad con la reivindicación 16 que incluye, además, tomar muestras de líquido cefalorraquídeo en un lugar subdural que es distinto del primer lugar subdural y medir la concentración del agente de curcumina en el líquido cefalorraquídeo para estimar la concentración del tejido cerebral.

5 20. Un método para reducir un trastorno del cerebro humano relacionado con la presencia de una sustancia patógena en el líquido cefalorraquídeo; el método comprende:

seleccionar un ser humano para tratarlo como paciente, al que se le ha diagnosticado con demencia;

10 colocar un extremo proximal de un primer catéter, que tiene por lo menos un primer lumen, en un primer lugar submeníngeo en el cerebro del paciente para establecer una comunicación abierta entre el primer lumen y el líquido cefalorraquídeo del paciente; y

15 por un periodo de tiempo prolongado, administrar un agente de curcumina seleccionado de por lo menos uno, entre un híbrido de curcumina y un análogo de curcumina, al líquido cefalorraquídeo para que interactúe con la sustancia patógena para atenuar su efecto en el cerebro, caracterizado además porque el agente de curcumina se libera desde un receptáculo conectado al primer catéter y alcanza una concentración de tejido cerebral de por lo menos 1 μM .

20 21. El método de conformidad con la reivindicación 20 que incluye, además, tomar muestras de líquido cefalorraquídeo en un lugar subdural que es distinto del primer lugar subdural y medir la concentración del agente de curcumina en el líquido cefalorraquídeo para estimar la concentración del tejido cerebral.