

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 February 2009 (05.02.2009)

PCT

(10) International Publication Number
WO 2009/018393 A2

(51) International Patent Classification:
A61N 2/00 (2006.01) A61N 1/36 (2006.01)
A61N 2/02 (2006.01)

(74) Agents: SHOOP, Richard, D. et al.; Shay Glenn, LLP,
2755 Campus Drive. Suite 210, San Mateo, CA 94403
(US).

(21) International Application Number:
PCT/US2008/071663

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 30 July 2008 (30.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/953,191 31 July 2007 (31.07.2007) US

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*):
NEOSTIM, INC. [US/US]; 112 Camerota Way, Redwood City, CA 64065 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): PARTSCH, Michael, J. [US/US]; 112 Camerota Way, Redwood City, CA 94065 (US). SCHNEIDER, M., Bret [US/US]; 10 Cordova Court, Portola Valley, CA 94028 (US). MISHELEVICH, David [US/US]; 7301 Vista Del Mar, B111, Playa Del Rey, CA 90293 (US).

Published:

— *with declaration under Article 17(2)(a); without abstract; title not checked by the International Searching Authority*

(54) Title: DEVICE AND METHOD FOR TREATING HYPERTENSION VIA NON-INVASIVE NEUROMODULATION

(57) Abstract:



WO 2009/018393 A2

DEVICE AND METHOD FOR TREATING HYPERTENSION VIA NON-INVASIVE NEUROMODULATION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 60/953,191, filed on July 31, 2007, titled "DEVICE AND METHOD FOR TREATING HYPERTENSION VIA NON-INVASIVE NEUROMODULATION."

INCORPORATION BY REFERENCE

[0002] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

FIELD OF THE INVENTION

[0003] The devices and methods described herein relate generally to the treatment of hypertension.

BACKGROUND OF THE INVENTION

[0004] Arterial hypertension, commonly referred to as "hypertension" or "high blood pressure", is a medical condition in which the blood pressure is chronically elevated. Hypertension is associated with markedly elevated risk of heart attack, heart failure, arterial aneurysms, kidney failure and stroke. Causes of hypertension in a given individual may be one or more of many possibilities, which may include salt intake, obesity, occupation, alcohol intake, smoking, family size, stimulant intake, excessive noise exposure, and crowding, renin levels, insulin resistance, sleep apnea, genetic susceptibility, decreased kidney perfusion, catecholamine-secreting tumors of the adrenal glands, Adrenal hypertension with

aldosterone-induced sodium retention, hypercalcemia, coarctation of the aorta, diet, medications, arterial stiffening that accompanies age. When the hypertension is secondary to another medical condition, it is generally prudent to treat that primary condition first. However, regardless as to whether the hypertension is primary or secondary, the blood pressure typically is subject to modification by several different approaches including changing (typically via medications) fluid excretion, heart activity, and blood vessel contraction.

[0005] Medications for blood pressure control are frequently not effective, or present troublesome side effects when raised to a therapeutic dose. Depending on the class of medication, such side effects range from the inconvenient to the deadly, and may include constipation, edema, exercise intolerance, impotence, orthostasis, syncope and stroke.

[0006] One frequently overlooked avenue for modifying blood pressure is control of the pressure by mechanisms intrinsic to the brain. The brain is a highly metabolically active organ with an immense need for oxygen-rich blood. When mechanisms within the brain sense low blood flow, mechanisms including those within the brain stem activate to raise overall blood pressure to levels adequate for perfusion of the brain, so as to avoid hypoxia. This may lead to a systemic hypertension.

[0007] Baroreceptors in the human body detect the pressure of blood flowing through them, and send messages to the central nervous system to increase or decrease total peripheral resistance and cardiac output, and thereby change blood pressure. There are baroreceptors in locations including the arch of the aorta, and the carotid sinuses of the left and right internal carotid arteries. Baroreceptors act to maintain mean arterial blood pressure to allow tissues to receive the right amount of blood. Neural signals from the baroreceptors are processed within the brain, in order to maintain physiological homeostasis. For example, the solitary nucleus and tract within the medulla and pons, receive signals from the carotid

and aortic baroreceptors. In response to a perception of low blood pressure, the solitary nucleus sends out signals leading to hypertension, tachycardia and sympatho-excitation. In response to a perceived state of high blood pressure, the opposite physiological response is triggered.

[0008] There are known methods for selectively increasing blood flow within the brain. One such method is transcranial magnetic stimulation (Speer et al 2000, Conca et al 2002, Takano et al 2004, Ohnishi et al 2004). The increased blood flow appears to occur as a result of the increased metabolic demands of activated neurons. Increased blood flow effect appears to be sustained long after the rTMS stimulus was received: In the case of rTMS-treated depression for example, the clinical benefit is closely associated with the enhance blood flow in the left dorsolateral prefrontal cortex, and appears to last for months before resuming its former pattern.

While it has been demonstrated that stimulation of the solitary nucleus with an implanted electrode serves to lower blood pressure, this method requires invasive brain surgery, the risks of which outweigh the benefits of treating hypertension in such a manner. The prior art does not show means by which blood pressure is lowered by non-invasive brain stimulation.

SUMMARY OF THE INVENTION

[0009] Described herein are methods and devices for treating hypertension by non-invasive techniques. In particular, described herein are devices and methods for treating hypertension by transcranial magnetic stimulation of one or more regions of a subject's brain. For example, described herein are methods for selectively modulating neuronal tissue so as to prompt central nervous system mechanisms to lower systemic blood pressure. These methods may include the steps of magnetically stimulating a brain region (e.g., using transcranial magnetic stimulation) to controllably trigger central homeostatic mechanisms, resulting the lowering of the subject's blood pressure drive. In direct modulation of blood

pressure using central homeostatic mechanisms, brain regions that may be targeted for stimulation include the superficial cortical aspects of the frontal lobes, the parietal lobes, the temporal lobes, the occipital lobes, or the cerebellum. For direct modulation of blood pressure, appropriate brain regions that may be stimulated include: solitary nucleus and tract or related brainstem circuitry.

[00010] As mentioned, stimulation may be transcranial stimulation. For example, transcranial stimulation may be electromagnetic pulses of approximately 1 Tesla in intensity, each lasting approximately 100 microseconds. Application of these pulses at frequencies of approximately 1 Hz to 25 Hz, for approximately 45 minutes, and repeated for several consecutive days generally serve to change activity level in the targeted brain region for 2-7 months.

[00011] In one embodiment, herein termed the “indirect” method, brain tissue is stimulated so as to increase its metabolic rate, leading to increased blood flow in the stimulated tissue. Secondly, central homeostatic mechanisms lower their blood pressure drive. In some variations, the subject may be monitored, and the stimulation linked to feedback from the subject.

[00012] In addition to stimulation by transcranial magnetic stimulation, other types of stimulation may be used. These may include ultrasound, pulsed electrical currents and direct electrical currents.

[00013] In an alternative embodiment, brainstem blood pressure homeostatic mechanisms are stimulated “directly” using transcranial brain stimulation. By this approach, the solitary nucleus or related circuitry within the brainstem is stimulated so as to directly inhibit blood pressure through intrinsic, dedicated physiological methods.

[00014] Pulse generation devices that produce such pulses are commercially available such as the Magstim Rapid stimulator by Magstim LTD (Wales, UK). When used with

commercially available coils such as the 70mm double coil (Magstim LTD (Wales, UK)), such stimulators may be used at rates of 5Hz or greater to increase blood flow in the cortical surfaces of the frontal, temporal, parietal and occipital lobes as well as in the cerebellum. This increase in blood flow may be used to increase blood flow to the targeted structures, thereby invoking the “indirect” method as herein described. When an array of stimulators, configured to power multiple coils simultaneously as herein described, stimulation may be targeted toward deeper, subcortical brain structures including the solitary nucleus and tract of the brainstem.

BRIEF DESCRIPTION OF THE DRAWINGS

- [00015] Figure 1 outlines the basic steps of the method described herein.
- [00016] Figure 2 illustrates examples of several exemplary anatomic locations for interventions in accordance with the methods herein described.
- [00017] Figures 3A and 3B illustrate the use of a multiple-coil array in order to stimulate the brainstem, in particular the solitary tract and nucleus.

DETAILED DESCRIPTION OF THE INVENTION

[00018] In general, methods of lower systemic blood pressure in accordance with the present invention include

[00019] 1) an “indirect” method in which overall cerebral blood flow is induced to rise using transcranial magnetic stimulation or other transcranial approach to the frontal, temporal, parietal, or occipital cortex, or to the cerebellum, thereby secondarily triggering to lowering of blood pressure regions, and

[00020] 2) a “direct” method in which the solitary nucleus and tract of the brainstem or related circuitry is directly stimulated using transcranial magnetic stimulation or other transcranial approach.

[00021] Figures 1A, 1B, and 1C outline the basic steps of some of the methods described herein.

[00022] In Figure 1A, a method is described in which increasing cerebral perfusion in general is used to effect an antihypertensive treatment. In step 105 a region of a hypertensive patient is studied, and a region of that patient's brain is selected to be the primary target for stimulation. This region could be the entire brain, for example using a large coil or a coil array that encircles the head, or could be a specific region, for example the brainstem. In step 110 that region is stimulated in a manner that is anticipated to increase blood flow in the brain or brainstem. Stimulation means may include repetitive transcranial magnetic stimulation (rTMS), stereotactic transcranial magnetic stimulation (sTMS) as described in US Serial No. 10/821,807, US Serial No. 11/429,504). Stimulation means may also include the implanted electrodes of deep brain stimulation (DBS) as is known in the art, superficial cortical stimulation grids, and transcranial direct current stimulation (tDCS) (Lang, et al 2005). Steps 115 through 130 describe the physiological responses that are evoked in response to targeted stimulations cited stimuli act upon those physiological circuits as described above. In step 115, the body is stimulated to increase the metabolism of the stimulated brain region. For example, in step 120, the body is stimulated to increase blood flow to the stimulated area. In step 125, stimulation proceeds until the brain detects this increased flow with its intrinsic pressure receptor and flow sensors. Areas in which these sensors are located are probably many, and include the solitary tract and nucleus (nucleus tractus solitarii) (Paton et al 2007, Waki et al 2007, Vayssettes-Courchay et al 1993). In step 130, the stimulation leads to detection of increased blood flow, triggering lower blood pressure through its intrinsic mechanisms, including downregulation of vascular tone, cardiac output, and blood volume.

[00023] Figure 1B outlines a method by which hypertension is treated by direct stimulation of the solitary nucleus and tract. In step 140, the solitary nucleus and tract are stimulated, for example magnetically using a transcranial magnetic stimulation as shown in the subsequent figures and description, for example at a pulse rate of 5Hz, 3500 pulses delivered per day for 20 consecutive weekdays. In step 145, the nucleus interprets this stimulation as signals of hypertension, in much the same manner that it normally interprets such activity as input from the baroreceptors in the carotid bodies and aortic bodies, and acts to lower blood pressure by its endogenous abilities based on the stimulation.

[00024] Figure 2 illustrates examples of two anatomic locations for interventions in accordance with the steps outlined in Figure 1A. TMS coil 220 and TMS coil 230 may be 70mm air-cooled double coil attached to a Rapid2 stimulator machine (Magstim Ltd., Wales, UK), and are shown in perspective to represent placement at an angle to the viewing plane. TMS coil 220 is centered over brain area target 235. TMS coil 230 is shown placed in a posterior parietal location, as an example of an alternate placement.

[00025] Figures 3A and 3B shows the use of multiple-coil arrays, like those described in "Robotic device for stereotactic transcranial magnetic stimulation." Schneider MB and Mishelevich DJ US Serial No. 10/821,807, and in "Trajectory-Based Transcranial Magnetic Stimulation" Mishelevich DJ and Schneider MB, Pending US Patent Application No. US Serial No. 11/429,504. In figure 3a, Coils 305, 310, and 315 surround the posterior aspect of the head, and may be moveable or stationary. In figure 3a the central coil 325 (equivalent to coil 305 in figure 3a) is shown in transparency. Solitary nucleus and tract 350 is shown in the lower pons and the medulla, roughly beneath the center of coil 325. Coil 320 and 330 are equivalent to coil 210 and 315, respectively.

REFERENCES

- [00026] Ohnishi T, Matsuda H, Imabayashi E, Okabe S, Takano H, Arai N, Ugawa Y. rCBF changes elicited by rTMS over DLPFC in humans. *Suppl Clin Neurophysiol.* 2004;57:715-20.
- [00027] Takano B, Drzezga A, Peller M, Sax I, Schwaiger M, Lee L, Siebner HR. Short-term modulation of regional excitability and blood flow in human motor cortex following rapid-rate transcranial magnetic stimulation. *Neuroimage.* 2004 Nov;23(3):849-59.
- [00028] Conca A, Peschina W, Konig P, Fritzsche H, Hausmann A. Effect of chronic repetitive transcranial magnetic stimulation on regional cerebral blood flow and regional cerebral glucose uptake in drug treatment-resistant depressives. A brief report. *Neuropsychobiology.* 2002;45(1):27-31.
- [00029] Speer AM, Kimbrell TA, Wassermann EM, D Repella J, Willis MW, Herscovitch P, Post RM. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biol Psychiatry.* 2000 Dec 15;48(12):1133-41.
- [00030] Paton JF, Waki H, Abdala AP, Dickinson J, Kasparov S. Vascular-brain signaling in hypertension: role of angiotensin II and nitric oxide. *Curr Hypertens Rep.* 2007 Jun;9(3):242-7.
- [00031] Vayssettes-Courchay C, Bouysset F, Verbeuren TJ, Laubie M. Role of the nucleus tractus solitarii and the rostral depressive area in the sympatholytic effect of 8-hydroxy-2-(di-n-propylamino)tetralin in the cat. *Eur J Pharmacol.* 1993 Sep 21;242(1):37-45. .
- [00032] Waki H, Liu B, Miyake M, Katahira K, Murphy D, Kasparov S, Paton JF. Junctional adhesion molecule-1 is upregulated in spontaneously hypertensive rats: evidence for a prohypertensive role within the brain stem. *Hypertension.* 2007 Jun;49(6):1321-7.
- [00033] Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, Rothwell JC, Lemon RN, Frackowiak RS. How does transcranial DC stimulation of the primary motor

cortex alter regional neuronal activity in the human brain? Eur J Neurosci. 2005 Jul;22(2):495-504.

[00034] “Robotic device for stereotactic transcranial magnetic stimulation.” Schneider MB and Mishelevich DJ US Serial No. 10/821,807

[00035] “Trajectory-Based Transcranial Magnetic Stimulation” Mishelevich DJ and Schneider MB, Pending US Patent Application No. US Serial No. 11/429,504

CLAIMS

What is claimed is:

1. A method for lowering human blood pressure comprising:
directing energy toward the neural tissue so as to increase brain metabolism
and blood flow, thereby lowering central blood pressure drive.
2. A method as in claim 1 wherein said energy source is transcranial magnetic stimulation.
3. A method as in claim 1 in which the solitary nucleus and tract signal to decrease the blood flow.
4. A method for treating hypertension comprising:
stimulating brain tissue so as to increase blood flow within the brain, thereby
raising central nervous system drive to decrease blood pressure.
5. A method for treating hypertension comprising:
stimulating brain tissue so as to increase blood flow within the brain, thereby
lowering central nervous system drive to increase blood pressure.
6. A method for treating hypertension comprising:
stimulating brain tissue so as to increase blood flow within the brain, thereby
raising central nervous system drive to decrease blood pressure.

1/2

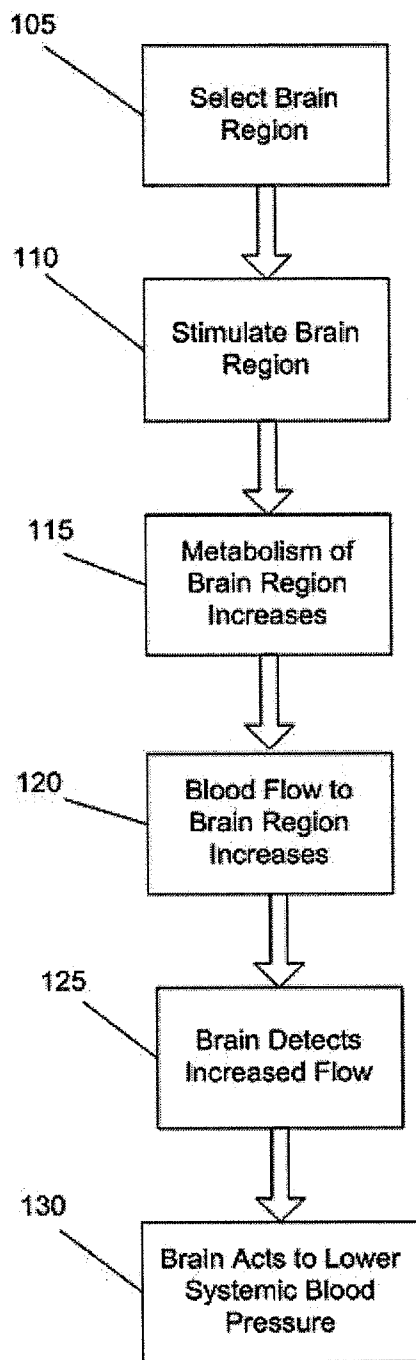


FIGURE 1A

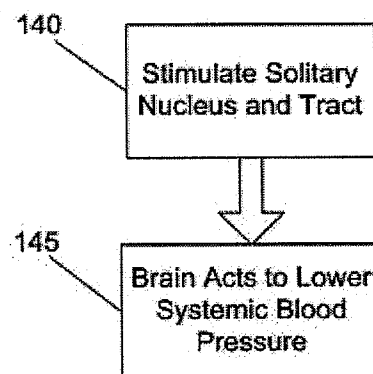


FIGURE 1B

2/2

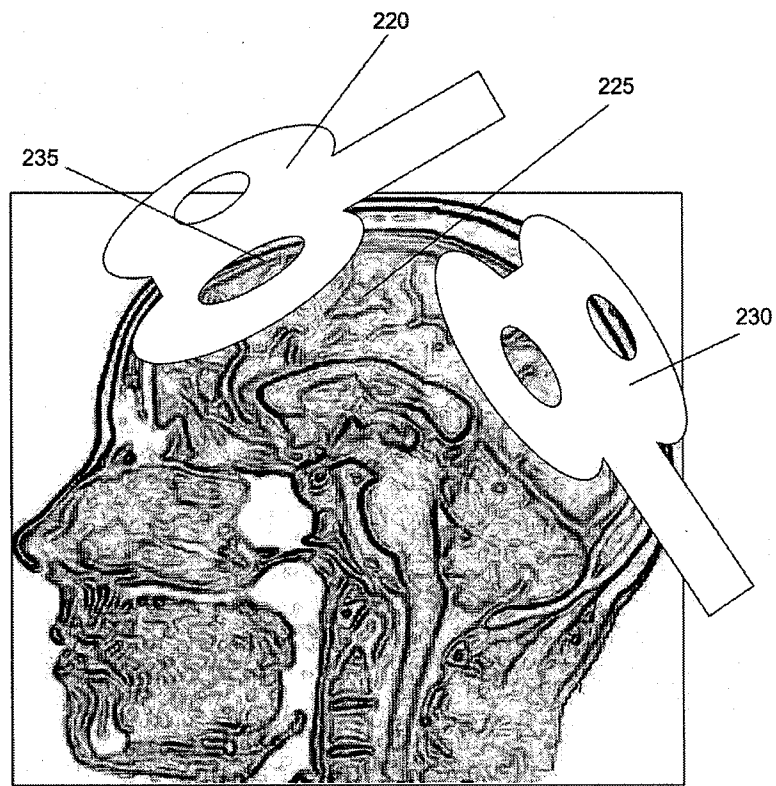


FIGURE 2

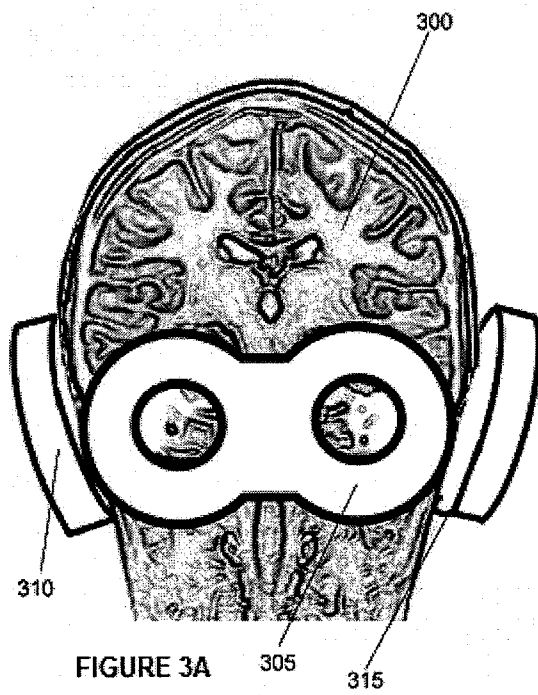


FIGURE 3A

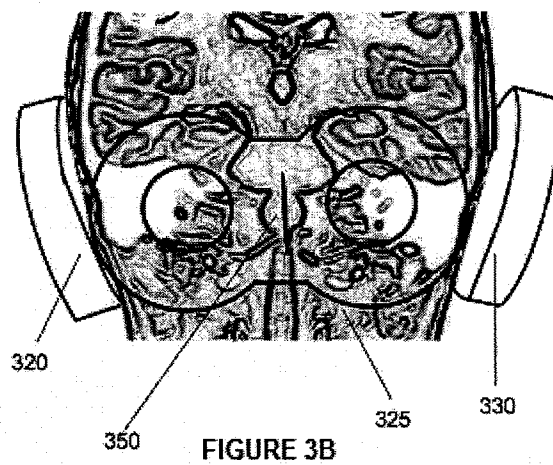


FIGURE 3B

PCT

(PCT Article 17(2)(a), Rules 13~~ter~~.1(c) and Rule 39)

Applicant's or agent's file reference 10851-700.600	IMPORTANT DECLARATION	Date of mailing(day/month/year) 24/11/2008
International application No. PCT/US2008/071663	International filing date(day/month/year) 30/07/2008	(Earliest) Priority date(day/month/year) 31/07/2007
International Patent Classification (IPC) or both national classification and IPC A61N2/00, A61N2/02, A61N1/36		
Applicant NEOSTIM, INC.		

1. ☒ The subject matter of the international application relates to:

- a. ☐ scientific theories
 b. ☐ mathematical theories
 c. ☐ plant varieties
 d. ☐ animal varieties
 e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes
 f. ☐ schemes, rules or methods of doing business
 g. ☐ schemes, rules or methods of performing purely mental acts
 h. ☐ schemes, rules or methods of playing games
 i. ☒ methods for treatment of the human body by surgery or therapy
 j. ☒ methods for treatment of the animal body by surgery or therapy
 k. ☐ diagnostic methods practised on the human or animal body
 l. ☐ mere presentations of information
 m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art
2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:
☐ the description ☒ the claims ☐ the drawings
3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:
☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
4. ☐ A meaningful search could not be carried out without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
5. Further comments:

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Eva San Miguel
--	--

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 203

A meaningful search is not possible on the basis of all claims because all claims are directed to methods for treatment of the human or animal body by therapy - Rule 39.1(iv) PCT.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.