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(54) Title: EXTERNAL ULTRASOUND GENERATING TREATING DEVICE FOR SPINAL CORD AND SPINAL NERVES TREATMENT, APPARATUS COMPRISING SUCH DEVICE AND METHOD IMPLEMENTING SUCH DEVICE

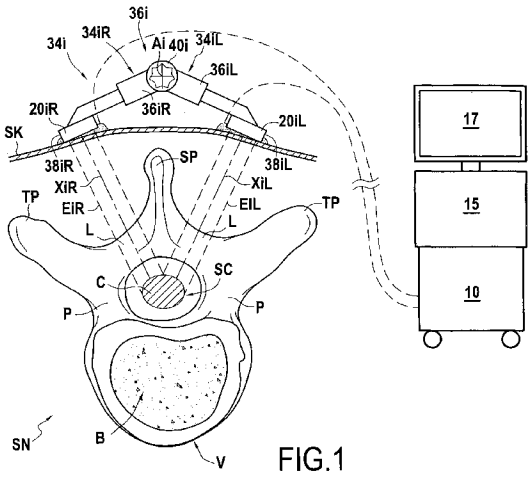

FIG.1

(57) Abstract: The invention related to an external ultrasound generating treating device (12), to induce spinal cord and/or spinal nerve treatment, comprising at least two sub-arrays of ultrasound generating treatment transducers, a left sub-array (20iL) being located on a left lateral side and a right sub-array (20iR) being located on a right lateral side of the central longitudinal axis (Ai), characterized in that the device comprises a support structure (32) having at least one module (34i) comprising a left lateral section (34iL) and a right lateral section (34iR), and in that the support structure (32) maintains, in use of the device, a constant distance and a constant relative angular orientation around the central longitudinal axis (Ai) between the first left and first right treatment transducers or set of treatment transducers (20iL, 20iR). The invention also provides for an apparatus including such a device and for methods.

EXTERNAL ULTRASOUND GENERATING TREATING DEVICE FOR SPINAL CORD AND SPINAL NERVES TREATMENT, APPARATUS COMPRISING SUCH DEVICE AND METHOD IMPLEMENTING SUCH DEVICE

Technical field

The present invention relates to a device, an apparatus and a method for the treatment of spinal cord and/or spinal nerve disorders, especially for the transient disruption of the blood-spinal cord barrier and/or blood-spinal nerves barrier of a human.

Background Art

The spinal cord and / or the spinal nerve(s) may to subject to various physiological disorders which induce different forms of pathologies. There is a clear need for improving therapies in this domain. Also, there is a need to improve the repair and/or rehabilitation treatments of the spinal cord and/or spinal nerve(s), for example for hemiplegia and paraplegia, including with cell transplant and/or stem cell regeneration.

Some available treatments include action of drugs on the spinal cord and/or spinal nerve tissues. However, the blood-spinal cord barrier (hereinafter BSCB) limits or prevents the penetration of therapeutic drugs in the spinal cord or nerve tissues. Similarly, the blood-spinal nerve barrier (hereinafter BSNB) prevents the penetration of therapeutic drugs in the spinal cord or nerve tissues.

It is known to use spinal drug delivery catheters inserted in the spinal canal, but this only allows injection of a fluid which only penetrates to a limited and insufficient extent into spinal cord or spinal nerve tissues.

Some documents suggest the use of spinal cord electrical stimulation, sometimes in association with drug delivery. US-6.319.241 describes techniques for positioning therapy delivery elements within a spinal cord or a

brain to provide electrical stimulation and/or drug infusion to a precise target. US-6862479 describes implantable system control units (SCU) to apply one or more stimulating drugs and/or electrical pulses to a spinal section responsible for innervating the male reproductive organs. Such methods do not cause any significant opening of the blood spinal cord barrier.

WO-96/39079 describes a method and an apparatus for performing ultrasonic imaging of a region of a patient while simultaneously applying therapeutic ultrasonic waves to the region for rupturing vesicles administered to that region, for purposes such as enhanced cavitation or the targeted release of a bioactive agent contained in the vesicles into the region.

Many systems and methods have been disclosed which rely on high energy ultrasounds for causing an intended damage to the targeted tissue. US-2005/0240170 describes methods and systems for producing hemostasis, tissue closure, or vessel closure by inserting a thermal delivery probe into a passageway and emitting thermal energy from the probe to produce the hemostasis or tissue closure. The thermal delivery probe may have one or more ultrasound transducers positioned in an elongated shaft. GR20070100349 discloses an ultrasound diathermy system that can be applied to the spinal cord. It causes a cut and hemostasis in the tissues, it seals vessels of relatively small transection without causing their rupture.

US-2008/0287837 discloses an interstitial end effector which is interstitially insertable into patient tissue, which includes at least one medical-treatment ultrasound transducer, and which includes at least one end-effector-tissue-track ablation device. US-2007/073135, describes an integrated ultrasound imaging and ablation probe. EP-1774989 discloses an ultrasound probe which comprises one or more transducers positionable on, in proximity to or within a cancerous mass of tissue. The one or more transducers are capable of delivering sufficient levels of acoustic energy to (a) induce coagulative necrosis of a region of the tissue surrounding the transducer, and (b) induce sonoporation of a chemotherapy agent into cancer cells in the tumor and in the margins of tissue adjacent the necrosis

region of tissue. EP-0643982 describes an ultrasound thermotherapy probe and method for treatment of prostate tissues. WO-2007/124458 describes a method of thermal treatment for myolysis and destruction of benign uterine tumors. JP-2007-289715 describes an ultrasonic diagnostic and therapeutic system in which high density ultrasonic energy can be concentrated and accurately irradiated on a desired position of a location to be treated.

WO-03/059437 describes a system and method for providing directional ultrasound therapy to skeletal joints, such as spinal joints. WO-03061756 describes a long-term implantable ultrasound therapy system and method is provided that provides directional, focused ultrasound to localized regions of tissue within body joints, such as spinal joints. US-2016/0016012 discloses an external stimulation apparatus using low intensity focused ultrasound, which has a low intensity ultrasound focusing array having a plurality of transducers for outputting low intensity ultrasound beams, and a fixing device to which the low intensity ultrasound focusing array is attached, the fixing device being configured to fix the low intensity ultrasound focusing array to an upper body of a user.

US-2015/0224345 discloses a method of treating a patient having a nerve injury or spinal cord injury or spinal cord lesions, comprising the steps of: activating an acoustic shock wave generator or source to emit acoustic shock waves from a shock wave head; and administering an effective exposure of acoustic shock waves in a pulse or wave pattern having a low energy density less than 1.0 mJ/mm2 per shock wave directly onto a treatment zone in a region extending from the medulla oblongata in the lower brain stem to the lower end of the spinal cord.

US-2005/0020945 discloses an apparatus including an emitter means to deliver acoustic, ultrasonic or vibratory energy in, into or from within a region of the patient's brain or spine which contains or is transportably-coupled to cerebrospinal fluid (CSF) or blood capable of bearing or bearing a chemical or biological species, reactant, fragment or byproduct of the disease.

US-8942781 describes a percutaneous probe, made in MRI-compatible materials, having : a body percutaneously inserted into the tissue of a patient's body organ having a region to be analyzed, treated and monitored during a single medical procedure; at least one information collection sensing device, treatment application transducers organized in a 360° fashion to emit focused or defocused therapeutic ultra-sound waves.

US-8977361 describes an apparatus for the treatment of a brain affection, which comprises at least one implantable generator made of non-ferromagnetic material comprising a casing, and an ultrasound generating treating device positioned into said casing to induce brain affection treatment by emission of ultrasound waves.

US-2015/0231417 discloses a method for treating a spine comprising the steps of: providing a magnetic resonance imaging (MRI) device; identifying a surgical site for treatment of a spinal disorder with the MRI device, the surgical site including a portion of a spine; providing a high intensity focused ultrasound (HIFU) device including a transducer for emitting ultrasound energy; determining parameters of treatment for the surgical site; and applying a dosage of ultrasound energy to the surgical site with the HIFU device for treating the disorder.

US-2013/0178765, US-2013/0281890 and US-2016/0001096 describe methods and systems for non-invasive neuromodulation of the spinal cord utilizing a transducer to deliver pulsed ultrasound energy to up regulate or down regulate neural targets for the treatment of pain and other disease conditions.

There remains the need for a system and a method capable of causing the transient disruption of the blood-spinal cord barrier and/or of the blood-spinal nerve barrier of a vertebrate subject. The specificity of these tissues and their location within the spine vertebrae, especially in the spinal canal, and the need to cause only a transient disruption of the blood-spinal cord barrier and/or of the blood-spinal nerve barrier in the targeted tissues, without damaging the targeted tissues, require a specific system and a specific method not yet available from the prior art.

Summary

The invention relates to an external ultrasound generating treating device to induce spinal cord and/or spinal nerve treatment by emission of ultrasound waves, wherein the ultrasound generating treating device is suitable for external positioning against the back of a patient, said device comprising an array of several ultrasound generating treatment transducers distributed along a longitudinal direction and a lateral direction, wherein the external ultrasound generating device comprises at least two sub-arrays of ultrasound generating treatment transducers, a left sub-array being located on a left lateral side of a central longitudinal axis and a right sub-array being located on a right lateral side of the central longitudinal axis, laterally opposite to the left side.

The external device is characterized in that it comprises a support structure having at least one module comprising a left lateral section holding at least a first left treatment transducer or set of treatment transducers of the left sub-array, and a right lateral section holding at least a first right treatment transducer or set of treatment transducers of the right sub-array, and in that the support structure maintains, in use of the device, a constant distance and a constant relative angular orientation around a longitudinal axis between the first left and first right treatment transducers or set of treatment transducers.

According to other optional features of such implantable device, taken alone or in combination:

- The support structure may comprise an adjusting mechanism for adjusting, around a longitudinal axis, a relative angular orientation between the left and right lateral sections of the support structure, so as to adjust the relative angular orientation around the longitudinal axis between the first left and first right treatment transducers or set of treatment transducers.
- The adjusting mechanism may comprise an articulation.

- The support structure may comprise an adjusting mechanism for adjusting a distance between the left and right lateral sections of the support structure, so as to adjust the distance between the first left and first right treatment transducers or set of treatment transducers.

- The adjusting mechanism may comprise a lock for maintaining, in use of the device, a constant distance and a constant relative angular orientation around the central longitudinal axis between the first left and first right treatment transducers or set of treatment transducers.

- The left and right lateral sections may have ultrasonic imaging transducers for forming respectively a left and a right image of an emission zone of the treatment transducer or set of treatment transducers held on the same section.

- The external ultrasound generating treating device comprises ultrasonic monitoring transducers.

- The support structure may comprise several modules arranged successively along the longitudinal direction, each module comprising a left lateral section, holding at least a left treatment transducer or set of treatment transducers of the left sub-array, and a right lateral section, holding at least a right treatment transducer or set of treatment transducers of the right sub-array, and the support structure maintains, in use of the device, a constant distance and a constant relative angular orientation around a longitudinal axis between the respective left and right treatment transducers or set of treatment transducers.

- Several modules have each an adjusting mechanism for adjusting, around a longitudinal axis, a relative angular orientation between the respective left and right lateral sections of the support structure, so as to adjust the angular orientation around a longitudinal axis between the first left and first right treatment transducers or set of treatment transducers.

- The adjusting mechanisms of several modules may be mechanically connected for simultaneous adjustment.
- At least two modules of the support structure may articulated to allow a relative angular movement between the two modules around an axis extending along the lateral direction.
- At least two modules of the support structure are articulated through a flexible module connector.

The invention also relates to an apparatus for inducing spinal cord and/or spinal nerve treatment by emission of ultrasound waves, characterized in that it comprises:

- an external ultrasound generating treating device having any of the above features;
- a generator to supply electricity to the external ultrasound generating treating device;
- a controller.

In such apparatus, the ultrasound generating treating external device may comprise left and right lateral sections of the external device having respective ultrasonic imaging transducers for forming respectively a left and a right image of an emission zone of the treatment transducer or set of treatment transducers held on the same section, and the controller may comprise an imaging module connected to the imaging transducers.

The invention also relates to a method for transiently opening the blood-spinal cord barrier and/or the blood spinal nerves barrier in at least one treatment zone of the spinal cord and/or spinal nerves of a patient, said method comprising :

- positioning externally against the back of the patient:
  - at least one left ultrasound generating treatment transducer or set of treatment transducers, having a left emission zone, on a left lateral side of the back of the patient with respect to the spine of the patient, and

• at least one right ultrasound generating treatment transducer or set of treatment transducers, having a right emission zone, on a right lateral side of the back of the patient with respect to the spine of the patient,

- forming at least one left image along a left imaging axis having a set orientation with respect to the left emission zone and one right image along right imaging axis having a set orientation with respect to the right emission zone;

- orienting the left and right emission zones according to the left and right images so that the left and right ultrasound emission zones are at least partially superposed on the treatment zone of the spinal cord or on the spinal nerves.

According to other optional features of such method, taken alone or in combination:

- Orienting the left and right emission may comprise orienting the treatment transducers or set of treatment transducers according to the left and right images so that the left and right ultrasound emission zones are at least partially superposed on the treatment zone of the spinal cord or on the spinal nerves.

- Orienting the left and right emission may comprise controlling the left and right treatment transducers or set of treatment transducers so as to electronically steer the left and right emission zones.

- The treatment zone may extend throughout the extension of several vertebrae of the patient.

- The method may involve the intravenous injection of an ultrasound contrast agent in the patient's blood circulation system, prior to and/or during the generation of the least one ultrasound treatment beam.

- The treatment ultrasound beam has a resonant frequency ranging from 0.5 to 4 MHz, preferably ranging from 0.75 to 2 MHz.

- The pressure level of the treatment beam may be determined to obtain a pressure level within the spinal cord and/or spinal nerve tissues between 0.8 MPa and 3.0 MPa.
- The applied treatment beam may have a mechanical index (MI) within the spinal cord and/or spinal nerve tissues of from 0.3 to 3.0.

Brief description of the drawings

The device, apparatus and method of the present invention will be further described in detail below with reference to the accompanying drawings showing preferred embodiments of the apparatus of the invention.

In the figures:

- **Figure 1** represents schematically an example of the positioning of a device according to the invention against the back of a patient, in cross-section though a transversal plane of the patient, viewed from the top;
- **Figure 2** represents schematically an embodiment of a module of device according to the invention;
- **Figure 3** and **4** represent schematically an example of the positioning of a device according to the invention, comprising several modules, against the back of a patient, respectively in back view and in lateral view;
- **Figure 5** represent schematically an enlarged view of a portion of the device of Figure 3.

Detailed description

On **FIG. 1** are shown the main components of an apparatus to induce spinal cord or spinal nerves treatment by emission of ultrasound waves,

comprising an exemplary embodiment of an external ultrasound generating treating device **12** according to the invention.

The apparatus comprises:

- an external ultrasound generating treating device **12**;
- an electrical generator **10** which generates electric signals to be delivered to the transducers of the external ultrasound generating treating device, where the generator may remain external to the body of the patient in use of the apparatus;
- a controller **15**, also external to the body, for example under the form of a computer, to set and control the working parameters of the generator.

According to an aspect of the invention, the external ultrasound generating treating device **12** is suitable for external positioning against the back of a patient who is awaiting the receipt of, or is receiving medical care or was/is/will be the object of a medical procedure, or is monitored for the diagnosis or the development of a disease. The patient can be any vertebrate subject, especially a mammal and in particular a human i.e., a person of the species Homo sapiens.

Fig. 3 to **5** illustrate schematically such a positioning in the case of a human patient. On those figures, one can see the spine **SN** of the patient, on the internal side of the skin **SK** of the back of the patient. The spine **SN** comprises vertebrae **V**. In a typical human vertebra, as shown on **Fig. 1** in a transverse cross-section perpendicular to the extension of the spine, a vertebra comprises a spinal canal **SC** portion which is delimited:

- towards the front by the vertebra body **B**,
- towards the sides by the two pedicles **P** which join the body **B** to the two transverse process **TP**, and
- towards the rear by the spinous process **SP** and the two laminas **L** which join each the spinal process **SP** to one of the two transverse processes **TP**.

The spinal cord **C** is located in the spinal canal and the spinal nerves (not represented) emerge from the spinal cord and extend laterally out of the spinal canal between two vertebrae.

More particularly, the external ultrasound generating treating device **12** is suitable for positioning, preferably directly on the skin, against the back, along the extension of at least a portion of the spine. A coupling agent, such as a gel, may be needed.

In operation, the generator **10** and the external ultrasound generating treating device **12** are to be connected electrically. Such electrical connection could be permanent. However, electrical connection is preferably a cable connection achieved through a connector device of the generator **10** and a connection receiver of the external treating device **12** which can be connected and disconnected, for example in the form of a plug-and-socket connection.

The external ultrasound generating treating device **12** comprises an array of several ultrasound generating treatment transducers distributed along a longitudinal direction and a lateral direction.

The treatment transducers generate focused or unfocused ultrasounds.

The ultrasound generating treatment transducers **20** are preferably chosen into the group formed by piezo-composite elements, piezo-ceramic elements, CMUT elements (Capacitive micro-machined ultrasonic transducers), or PVDF elements (Poly(vinylidene fluoride)). Piezo-composite elements or piezo-ceramic elements usually have a size in the range of 1 to 50 mm in diameter. CMUT elements usually have a size in the range of 10 to 50 µm in diameter. Piezoelectric components are commonly used in the medical field as ultrasound transducers. A given transducer can comprise one or several discrete elements which are activated simultaneously.

The ultrasound treatment transducers have an ultrasound generating resonant frequency which is preferably comprised between 0.5 and 4 Mhz, more preferably between 0.75 and 2Mhz for achieving transient disruption of the blood-spinal cord barrier and/or of the blood-spinal nerve barrier of the targeted portion of the spinal cord and/spinal nerve(s).

In most commonly used ultrasound generating transducers, the ultrasound energy is generated by virtue of the vibration created in the core of the transducer by an alternating voltage by virtue of a piezoelectric effect

or capacitive variation. The transducer is fed with an electric voltage which may have a given frequency or which may have a frequency spectrum which may be decomposed into preferably a limited number of main frequencies. The core of the transducer may thus be designed such that it exhibits at least one inherent resonant frequency.

A resonant frequency of the transducer can be defined as the frequency of the drive signal for which the ratio of the acoustic power output divided by consumed electrical power reaches a maximum (at least within neighbouring frequencies). For a typical piezoceramic transducer, this ratio is typically between 50% and 90% at a resonant frequency. If the electric current fed to the transducer exhibits such frequency, it will induce in the transducer a resonant vibration which will generate ultrasound. If the electric current fed to the transducer exhibits only a frequency or frequencies which lie outside of a resonant range around the resonant frequency, then the acoustic power output will be less than 25% of the power delivered when driven with a given voltage at its resonant frequency.

It must be noted that the term resonant frequency, as used in this text, covers an individual peak resonant frequency, at which the transducer **20** delivers a peak ultrasound field power/intensity for a given electric drive signal power, or a resonant frequency range, around such peak resonant frequency, for which the transducer **20** delivers a ultrasound field power/intensity higher than a minimum field power/intensity, which may be expressed as a percentage of the peak ultrasound field power/intensity.

A transducer may have a given operating frequency by choosing for example its resonant thickness along a given direction along which the ultrasound waves are to be emitted. For example thickness for a 1 MHz transducer for PZ26 material should be at 2 mm along the desired direction of emission.

The frequency content of the electric drive signal can be obtained directly, in case of a simple alternating voltage having one frequency, such as a pure sinusoidal signal. It can also be obtained through Fast Fourier Transform (FFT), as known to the man skilled in the art of signal processing.

It can be noted that, the intensity/power of the ultrasound field generated by a given transducer will depend on the amplitude of the electric drive signal delivered by the generator **10** at the operating frequency.

In use, the external ultrasound generating treating device **12** is intended to be positioned against the back of the patient with its longitudinal direction parallel to the elongation line of the spine, i.e. in the sagittal plane of the patient, and its lateral direction extending perpendicularly to the longitudinal direction, parallel to the axial and coronal planes of the patient.

More precisely, the array of several ultrasound generating treatment transducers comprises at least two sub-arrays of ultrasound generating treatment transducers, a left sub-array being located on a left lateral side of a central longitudinal axis and a right sub-array being located on a right lateral side of the central longitudinal, laterally opposite to the left side.

The external ultrasound generating treating device **12** comprises a support structure **32** having at least one module **34i**, one of which can arbitrarily be named a first module, each module comprising a left lateral section **34iL**, holding at least a first left treatment transducer **20iL** or set of treatment transducers of the left sub-array, and a right lateral section **34iR** holding at least a first right treatment transducer **20iR** or set of treatment transducers of the right sub-array. It will be seen that the support structure **32** preferably comprises several modules, preferably several modules **34i** having the same features.

The left and right lateral sections **34iL**, **34iR** of a module **34i** of the support structure **32** preferably comprise each a support member which holds respectively the first left treatment transducer **20iL** or set of treatment transducers and the first right treatment transducer **20iR** or set of treatment transducers. The support member of a given module section **34iL**, **34iR** and the arrangement of the treatment transducers on that support member are preferably rigid enough so that, in use of the device, i.e. when exposed to the normal forces involved in normal use, there is no movement of the transducers relative to the support member and, if applicable, no relative

movement between the set of transducers of a given module section **34iL**, **34iR**.

The support structure **32** maintains, in use of the device, a constant distance and a constant relative angular orientation around a longitudinal axis, e.g. the central longitudinal axis **Ai** of the module **34i,** between the first left and first right treatment transducers or set of treatment transducers **20iL**, **20iR**. In other words, the support structure holds the left and right treatment transducers or set of treatment transducers **20iL**, **20iR** rigidly enough to maintain, during use, a constant distance and relative angular orientation between the first left and first right treatment transducers or set of treatment transducers **20iL**, **20iR**.

As will be seen, a given module **34i** of the support structure **32** may be arranged in the external ultrasound generating treating device **12** so that its central longitudinal axis **Ai** extends along or parallel to the longitudinal direction of the external ultrasound generating treating device **12**.

In use, i.e. at least during the duration of application of an ultrasound treatment beam to the patient as will be described below, the first left and first right treatment transducers or set of treatment transducers **20iL**, **20iR** have no relative movement and keep a same relative spatial configuration. This same spatial relative configuration is maintained even in spite of the patient having small movements during the application of the ultrasound treatment beam, including movements due to the patient breathing.

The constant distance is preferably maintained between any two points of the first left and first right treatment transducers or set of treatment transducers **20iL**, **20R**.

An ultrasound generating treatment transducer **20iL**, **20iR** can be considered to have a given ultrasound emission zone, typically in the form approximately of a cylinder or a cone in which the intensity of the ultrasound field is significant. For a set of treatment transducers of a given module section **34iL**, **34iR**, the combined treatment transducers thereby generate a

combined section emission zone, which can be assimilated, for the purpose of the invention, to an emission zone of a combined transducer. For example, in **Figure 1** is shown the case of said field of an external ultrasound generating device **12** having left and right treatment transducers or set of treatment transducers **20iL**, **20iR**. Each left and right treatment transducers or set of treatment transducers **20iL**, **20iR**, when properly activated at its operating frequency, delivers an ultrasound field which can be characterized by a border emission envelope **EiL**, **EiR** which is shown here as a cylinder or a cone having a central axis **XiL**, **XiR**. The border emission envelope of the emission zone **EiL**, **EiR** can be defined as the envelope containing all locations where the acoustic pressure of the ultrasound field generated by the corresponding left and right treatment transducers or set of treatment transducers **20iL**, **20iR** is equal to at least a certain percentage, for example 25%, of the ultrasound field, at the same distance from the transducer, along a direction of maximum acoustic pressure. In real-world examples, the border envelope is not exactly a cylinder or a cone but, for the type of transducers used in the field of medical treatment ultrasound, can be considered as fairly close to a cone, or at least may be comprised in such a cone. Thus, the treatment transducers may have an ultrasound emission zone comprised in a cone having a central emission axis **XiL**, **XiR** as its axis of symmetry. Such cone has preferably an opening angle less than 30 degrees.

As can be seen on **Fig. 1**, the treatment transducers are respectively arranged on their respective module sections so that the emissions zones of the left and right treatment transducers or set of treatment transducers **20iL**, **20iR** are targeted towards the spinal canal when the external device **12** is positioned along the spine of a patient, against the back the patient. Therefore, the central emission axis **XiL**, **XiR** of the corresponding left and right emission zones is preferably perpendicular to the longitudinal direction. In a plane perpendicular to the longitudinal direction, the left and right emission zones are preferably directed so as

converge on the spinal canal when the external device **12** is positioned along the spine of a patient, against the back the patient.

The constant distance and relative angular orientation between the first left and first right treatment transducers or set of treatment transducers **20iL**, **20iR** induces that the emission zones, including the combined emission zone if applicable, of the first left and first right treatment transducers or set of treatment transducers **20iL**, **20iR** keep a same relative spatial configuration, when the external device **12** is positioned along the spine of a patient, against the back the patient. In other words, in use of the device, the support structure is rigid enough between the left and right sections of a given module in order that the support structure does not deform when subject to the normal forces endured during normal use of the device.

For example, as in the shown embodiment, each section of the module may comprise a support member having a rigid arm **36iL**, **36iR** extending laterally, the two arms **36iL**, **36iR** being connected at a respective proximal end, and a respective transducer bracket **38iL**, **38iR** rigidly connected at their respective distal ends. The brackets may be in the form of rigid plate like elements. Such brackets preferably extend along a limited width according to the lateral direction, for example less than 5 cm, preferably less than 3 cm. Such brackets preferably extend along a length according to the longitudinal direction which is preferably comprise between 1 cm and 15 cm, preferably between 3 cm and 10 cm. The arms **36iL**, **36iR** may form an arch extending laterally between the transducer brackets **38iL**, **38iR**. The brackets are preferably spaced apart with their facing edges laterally distant by at least 1cm, preferably at least 3 cm.

In some embodiments, for a given module **34i** of the support structure **32**, the relative sections **34iL**, **34iR** have a non-adjustable relative spatial configuration, including a constant distance and relative angular orientation. Such non-adjustable relative spatial configuration **34iL**, **34iR** of the relative sections **34iL**, **34iR** may be set once and for all, for example at the moment of manufacture of the external device **12**. In such a case, the

the two arms **36iL, 36iR** of pertaining to the respective sections of a module **34i** may be joined at their proximal end so as to form a single rigid and non-adjustable part, for example in form of arigid arch.

Such a non-adjustable module is thus then designed in view of predefined geometry of an expected patient's anatomy, so that the left and right emission zones are preferably directed so as converge on the spinal canal when the external device **12** is positioned along the spine of a patient, against the back the patient.

However, in some embodiment of the invention, the support structure of a given module **34i** may comprise an adjusting mechanism **36i** for adjusting the relative spatial configuration of the left and right sections **34iL, 34iR** of the module **34i**. This allows for a more precise targeting of the ultrasound treatment beam on the spinal cord and/or a spinal nerve.

Such adjustment may include the adjustment, around a longitudinal axis, e.g. the central longitudinal axis **Ai** of the module **34i**, of a relative angular orientation between the left and right lateral sections **34iL, 34iR** of the support structure **32**, so as to adjust the angular orientation around the central longitudinal axis **Ai** between the first left and first right treatment transducers or set of treatment transducers **20iL, 20iR.**

The adjusting mechanism may comprise an adjustment articulation **36i.**

In some embodiments, a single adjustment articulation **36i** may be provided between the two sections **34iL, 34iR** of a given module **34i.** As in the example, such single articulation **36i** may be located centrally, at the proximal end of the arms **36iL, 36iR.**

In some embodiments, an adjustment articulation **36i** may be provided in each of the two sections **34iL, 34iR** of a given module **34i,** for example between the bracket **38iL, 38iR** and the distal end of the corresponding arm **36iL, 36iR.**

An adjustment articulation **36i** may comprise a mechanical articulation comprising two rigid parts having a relative motion along respective sliding surfaces, such as a pivot or ball joint connection.

An adjustment articulation **36i** may be of the type having two or three rotational degrees of freedom, for example around two or three perpendicular articulation axes, including the central longitudinal axis **Ai** of the module **34i** or another longitudinal axis parallel thereto.

However, as shown in the depicted embodiments, an adjustment articulation may be of the type having only one degree of freedom, for example around only a longitudinal axis, e.g. the central longitudinal axis **Ai**, with no other possible rotational movement between the two sections **34iL**, **34iR** of the module **34i**.

Similarly, the support structure **32** may comprise an adjusting mechanism for adjusting a distance, for example along a lateral direction of the module, between the left and right lateral sections **34iL**, **34iR** of the support structure of the module **34i**, so as to adjust the distance between the first left and first right treatment transducers or set of treatment transducers of that module **20iL**, **20iR**. For example, in the example shown, the arms of the support member in each section may be telescopic and adjustable in length. Alternately, the brackets could be attached to the arms in an adjustable manner along the extension of the arm.

Preferably the adjusting mechanism **36i** comprises a lock **40i** for maintaining, in use of the device, a constant distance and a constant relative angular orientation around the central longitudinal axis between the first left and first right treatment transducers or set of treatment transducers. The lock may comprise a tightening screw tightening the adjustment mechanism in a desired position. The lock may thus allow locking of the adjustment mechanism in any position in a range of positions, to allow continuous adjustment of the relative spatial configure of the two sections of the module 34i with a range of relative spatial configurations. The lock may comprise indents allowing locking only in predefined spatial configurations.

The optimum relative spatial configuration of the left and first right treatment transducers or set of treatment transducers **20iL**, **20iR** of a given module is dependent on the expected anatomy of a patient.

For an external ultrasound generating treating device **12** intended for use on an adult human, a range of adjustment of the angular orientation, around the central longitudinal axis **Ai,** between the first left and first right treatment transducers or set of treatment transducers **20iL**, **20iR**, is preferably of at least 30 degrees, preferably of at least 60 degrees.

For an external ultrasound generating treating device **12** intended for use on an adult human, a range of adjustment of the distance, along a lateral direction of the module, between the first left and first right treatment transducers or set of treatment transducers **20iL**, **20iR**, is preferably of at least 50 millimeters, preferably of at least 100 mm.

Having an optimal spatial configuration of the left and right treatment transducers or set of treatment transducers, and maintining this optimal spatial orientation is an important aspect. An optimal spatial configuration is for exemple achieved when the left and right emissions zones of the left and right treatment transducers or set of treatment are at least partially superposed on the treatment zone of the spinal cord or on the spinal nerves of the patient. Even more optimal is to have the left and right emissions zones transducers intersecting a portion of minimum thickness of the lamina of the vertrebrae before hitting the the spinal cord or on the spinal nerves of the patient.

In non-adjustable modules, a proper design allows an adapatation of the device to an average patient anatomy, already allowing in most cases that a good portion of the left and right emission zones avoid at least the spinous process and the transverse processes of the vertebrae.

Having transducers coming from both the left and the right side and targeted at the same treatment zone of the spinal cord or on the spinal nerves of the patient allows a better handling of the diffraction effects.

However, modules having an adjustment mechanism allow a perfect adaptation of the external device to the patient's real anatomy, and thus allows the most optimal ultrasound treatment conditions. Once an optimal adjustment is determined and set, it is maintained during the used of the device, for example by locking the adjusting mechanism with a lock.

In some embodiments, the left and right lateral sections **34iL**, **34iR** of a given module **34i** of the external ultrasound generating treating device **12** may have ultrasonic imaging transducers **42iL, 42iR** for forming respectively a left and a right image of an emission zone of the treatment transducer or set of treatment transducers **20iL**, **20iR** held on the same section. Such images are typically digital images obtained from the ultrasound information collected by the ultrasonic imaging transducers **42iL**, **42iR**. The imaging transducers may be of any suitable conventional type known to the skilled man in the art. They may have an operating frequency comprised between 200KHzz and 20 GHz, preferably from above 2GHz to 20 GHz. Each ultrasonic imaging transducer **42iL, 42iR** may be formed of one or several individual transducers. They may be held by the same support member as the treatment transducers, for example the brackets **38iL, 38iR**. The relative configuration of the ultrasonic imaging transducers **42iL, 42iR** with respect of to the treatment transducer or set of treatment transducers **20iL**, **20iR** held on the same section is preferably fixed, but may be different to the schematic shown on **Fig. 2**.

The external ultrasound generating treating device **12** may comprise ultrasonic monitoring transducers **44iL**, **44iR**, for example wideband ultrasonic transducers. Monitoring transducers may be flexible membrane transducers. Monitoring transducers are preferably able to pick-up an ultrasound signal over a wide frequency range, ideally between 50 kHz and 50 Mhz. Such monitoring transducers may be tailored and used for monitoring cavitation due to the ultrasonic treatment.

A module **34i** could be of limited extension the longitudinal direction, for example corresponding to the length of a single vertebra of a patient and adapted to treat a treatment zone of comparable extension. It could be longer along that direction, for example corresponding to the length of several vertebrae of a patient and adapted to treat a treatment zone of comparable extension.

An external ultrasound generating treating device **12** may comprise a single module as described above.

Preferably, as shown on **Figs. 2** to **5**, the support structure 32 comprises several modules **34i** arranged successively along the longitudinal direction, each module **34i** having one or several of the above features. Each module **34i** comprises a left lateral section holding at least a left treatment transducer or set of treatment transducers of the left sub-array, and a right lateral section holding at least a right treatment transducer or set of treatment transducers of the right sub-array. As described above, the support structure maintains, in each module **34i**, in use of the device, a constant distance and a constant relative angular orientation around the central longitudinal axis of the respective module between the respective left and first treatment transducers or set of treatment transducers of said module **34i**.

All the modules **34i** could have the same size. However, it can be provided that different modules **34i** could be of different sizes depending on their location along the longitudinal direction of the external device **12**.

All of the modules **34i** could have the same features. However, it can be provided that different modules **34i** could have a different set of features amidst the above described features.

Preferably several modules **34i** have each an adjusting mechanism **34i** for adjusting, around their respective central longitudinal axis, a relative angular orientation between the respective left and right lateral sections of the support structure, so as to adjust the angular orientation around the central longitudinal axis between the first left and first right treatment transducers or set of treatment transducers of that module **34i**.

In such a case, the adjusting mechanisms **36i** of several modules **34i** may be advantageously mechanically connected for simultaneous adjustment. The simultaneous adjustment of the several modules **34i** can follow a predefined relative variation.

In an external ultrasound generating treating device **12** having a support structure **32** comprising several modules **34i** arranged successively along the longitudinal direction, at least two modules **34i** of the support structure **32** may be articulated to allow a relative angular movement between the two modules around an axis extending along the lateral direction. Such an example is represented on **Figs 3** to **5**. Upon positioning of the external device against the back of a patient, such device can thus adapt and conform to the shape of the spine, as particularly visible on **Fig. 4**.

Two successive modules **34i** may be articulated though a single or several inter-module articulation(s) **46**, arranged in parallel or in series.

Two successive modules **34i** may be articulated with only one degree of freedom, for example around only one laterally extending axis **Bi**, with no other possible rotational movement between the two modules **34i**. However, two successive modules **34i** may preferably be articulated with several degrees of freedom. Preferably the modules are articulated so that some degree of twisting around the longitudinal axis is also possible, in addition to an articulation around the lateral axis. Furthermore, the connection between two modules preferably additionally allows a relative displacement, along a direction perpendicular to the lateral and longitudinal directions, of two facing laterally extending edges of two consecutives modules.

An articulation may comprise a mechanical articulation comprising two rigid parts having a relative motion along respective sliding surfaces, such as a pivot or ball joint connection.

However, as shown in the depicted embodiments, at least two modules **34i** of the support structure **32** are articulated through one or several flexible module connector **46**. A flexible module connector **46** may be a sheet of flexible material, extending preferably in a longitudinally and laterally extending plane, or a cable, extending preferably along the longitudinal direction. A flexible module connector **46** may be elastic along the longitudinal direction, or to the contrary it may be inelastic so as to

define a set maximum distance between two consecutive modules **34i** along the longitudinal direction.

In the shown embodiment, the support structure of the external device is symmetrical with respect to a plane of symmetry which extends longitudinally and perpendicularly to the lateral direction. In use, this plane of symmetry is preferably aligned with the spine of the patient.

The left and right sections of a module are each connected respectively to the left and right sections of consecutive modules along the longitudinal direction by a respective flexible module connector **46**, here under the form of a sheet of flexible material, extending preferably in a longitudinally and laterally extending plane. The flexible module connectors **46** between two successive modules are here arranged in parallel, spaced apart along the lateral direction on each side of longitudinal axis.

Each flexible module connector **46** has a length along the longitudinal direction which is preferably of at least 10 mm, more preferably at least 20 mm, to allow sufficient flexibility and relative movement between two consecutive modules.

The external ultrasound generating treating device **12** also comprises an electrical connection network for connecting the ultrasound generating transducers **20** to the generator **10** delivering electric drive signals. The electric connection network may comprise one or several electrically independent electric connection circuits, where it will be understood that a given electric connection circuit is a circuit where a common electric drive signal is circulating. An independent electric connection circuit may be used to drive a single treatment transducer or may be used to drive a group of treatment transducers. Each independent electric connection circuit will have its own independent electric connection to the generator **10** and the generator may deliver separate and different electric drive signals to each independent electric connection circuit. For example it can be provided that each module has its own independent electric connection circuit, which may be shared between its left and right sections. Independent electric

connection circuit may be useful for addressing possible impedance variation between transducers.

In any case, imaging transducers and/or monitoring transducers, if present, would preferably have their own separate electric connection circuit.

Preferably, the external ultrasound generating treating device **12** is made of non-ferromagnetic materials, preferably MRI compatible materials.

The generator **10** is adapted for delivering electric drive signals to be delivered to the ultrasound generating treatment transducers **20** of an associated ultrasound generating treating device **12**. The generator typically comprises an alternating voltage generator able to generate an electric signal, for example a sinusoidal electric voltage signal. One example of a generator system that can be used with the inventive device may include a system that integrates signal generation, amplification, and control into a single unit. However, a generator system can also comprise one or several individual components performing one or more of these functions. For example, the generator can include an HP/Agilent 33120 function generator. If needed, it can also include for example one or more of an ENI 240L Broadband RF amplifier, of a Rhode and Schwarz RF power meter, and /or external computer controlling equipment over GPIB/Serial/USB interfaces.

Therefore, the controller **15** may comprise a computer. A computer human/machine interface **17**, for example a keyboard, and/or mouse and/or a display and/or a touchscreen interface, can be provided to control the system and give the user feedback. A radiofrequency board that generates the RF signal and amplifies it may be provided, as well as a coupler to measure the delivered RF power, and matching components to tune the generator output to the impedance of the ultrasound elements. Preferably, the generator **10** may be of a type capable to deliver 25-100 W peak RF power, capable of sending burst lengths with durations of 1 microsecond to continuous mode, and capable of sending bursts within the frequency range of 200 kHz to 2 MHz. Such a system can be controlled to send pulses with variable frequency and duty cycles for durations of approximately 2-5 minutes. The generator may be a class A/B RF system, which means that it is

capable of generating nearly pure sinusoidal signals, but this may make the system rather large. In some embodiments, the generator could be a class D system, which tends to generate signals that are square wave on the output.

As seen on **Fig. 2**, the controller **15** may comprise a treatment control module **15A** for controlling the generator in view of providing the adequate electric drive signals to the treatment transducer or set of treatment transducers **20iL**, **20iR** of the external ultrasound treating device **12**.

The controller **15** may also comprise an imaging module **15B** connected to the imaging transducers **42iL**, **42iR** of the external ultrasound treating device **12**, if provided with such imaging transducers. The imaging module **15B** may be configured to display one or several images on a display **17**, and/or to provide data extracted from a controller performed analysis of the images.

The controller **15** may also comprise a monitoring module **15C** connected to the monitoring transducers **44iL**, **44iR** of the external ultrasound treating device **12**, if provided with such monitoring transducers. The monitoring module **15C** may be configured to display one or several images on a display **17**, and/or to provide data extracted from a controller performed analysis of the ultrasound signal collected by the imaging transducers.

According to another aspect of the invention, it is provided a method for transiently opening the blood-spinal cord barrier and/or the blood spinal nerves barrier in at least one treatment zone of the spinal cord and/or spinal nerves of a patient.

In the context of the invention, the terms "disrupting", "opening" or "increasing the permeability" of the BSCB or BSNB are used interchangeably to refer to an increased susceptibility of the BSCB or BSNB to the passage of molecules therethrough that occurs without detectable damaging of the spinal cord or spinal nerve tissue.

In the context of the invention, a "transient" opening refers to a reversible opening occurring preferably for more than 1 hour, the BSCB or

BSNB returning after that to its initial state (i.e., the BSCB or BSNB state before the application of the first ultrasound treatment beam).

In some embodiments, the BSCB or BSNB opening occurs for a period of time from 1 to 48 hours, preferably from 5 to 24 hours, more preferably from 6 to 10 hours. In some embodiments, the BSCB or BSNB opening occurs for approximately 8 hours.

In some embodiments, the BSCB or BSNB disruption is delimited, i.e., occurs solely in a target region of the BSCB or BSNB. For instance, only a region of the BSCB or BSNB surrounding damaged spinal cord or spinal nerve tissue, such as a tumor, is targeted. In other embodiments, the BSCB or BSNB disruption is generalized.

The disruption may be easily confirmed and/or evaluated by magnetic resonance imaging (MRI). For example, a gadolinium-based magnetic resonance (MR) contrast agent such as Dotarem® (gadoterate meglumine, Guerbet USA), which does not normally cross the BSCB or BSNB, can be used to visualize the region of BSCB or BSNB disruption. When the agent is injected in a patient, a T1w MR sequence can be used to visualize regions of hypersignal and therefore visualize the effect of BSCB or BSNB disruption by ultrasound. BSCB or BSNB disruption typically leads to a change of 5-10% or more in MR signal enhancement after contrast agent administration. With the invention, a change of more than 25%, preferably more than 50% in MR signal enhancement after contrast agent administration is contemplated. In addition, dynamic contrast enhanced (DCE) MR imaging techniques can be used to calculate the permeability of the BSCB or BSNB and to quantify the magnitude of the permeability enhancement after ultrasound treatment.

The method can be used for delivering substances into targeted spinal cord or spinal nerve tissue of the subject and/or for treating a the spinal cord or spinal nerve disease.

The method can be used to treat various physiological disorders which induce different forms of pathologies including;

- spinal degenerative pathologies, such as amyotrophic lateral sclerosis (ALS)

- spinal cord tumor diseases, such as spinal astrocytomas
- spinal inflammatory pathologies, such as multiple sclerosis, etc...

It can also be used to improve the repair and/or rehabilitation treatments of the spinal cord and/or spinal nerve(s), for example for hemiplegia and paraplegia, including with cell transplant and/or stem cell regeneration.

The method preferably comprises positioning externally against the skin of the back of the patient:

- at least one left ultrasound generating treatment transducer or set of treatment transducers, having a left emission, on a left lateral side of the back of the patient with respect to the spine of the patient, and
- at least one right ultrasound generating treatment transducer, having a right emission zone, on a right lateral side of the back of the patient with respect to the spine of the patient.

Such method can thus be implemented with an external ultrasound generating treating device **12** as described above.

As explained above, it can be considered that each treatment transducer or set of treatment transducers has an ultrasound emission zone comprised in a cone having a central emission axis as its axis of symmetry.

The method further comprises forming at least one left image along a left imaging axis having a set orientation with respect to the left emission zone and one right image along a right imaging axis having a set orientation with respect to the right emission zone of the left and right treatment transducers or set of treatment transducers. The imaging axis can be the axis joining the center of the imaging transducer or set of imaging transducers to the center of the object which is imaged by the imaging transducer or set of transducers. Such set orientation may be obtained by having a left and right imaging axis corresponding respectively to the left and right central emission axis of the left and right emission zones.

Advantageously, the method provides for orienting left and right emission zones according to the left and right images so that the left and

right ultrasound emission zones are at least partially superposed on the treatment zone of the spinal cord or on the spinal nerves. Of course, such method is most conveniently implemented with an external device as described above wherein the support structure of a given module **34i** comprise an adjusting mechanism **36i** for adjusting the relative spatial configuration of the left and right sections **34iL**, **34iR** of the module **34i**. Indeed, adjustment of the left and right sections **34iL**, **34iR** of the module **34i** is made simply and precisely thanks to the adjustment mechanism, before or at the beginning of the treatment, and the relative configuration is reliably maintained during the treatment.

However, even in the case of an external device having one or several modules not having such adjusting mechanism, but having a left and a right set of treatment transducers, it is also possible to orient the left and right emission zones. In such a case, it is possible to orient the left and right emission zones by controlling the left and a right set of transducers so as to electronically steer the left and right emission zones. Such technique is conventionally called "electronic beam steering". Such technique can involve introducing time delays between the electric drive signals sent to the individual treatment transducers within respectively the left and right sets of treatment transducers. The time delays may be computed to steer the beam in one direction or the other. In any case, electronic beam steering can also be implemented with external devices having an adjusting mechanism according to the invention, thus in addition to the adjustment of the relative angular orientation between the left and right lateral sections of the support structure.

Even more preferably, such method is most conveniently implemented with an external device as described above wherein the support structure of a given module **34i** comprise an adjusting mechanism **36i** for adjusting the relative spatial configuration of the left and right sections **34iL**, **34iR** of the module **34i**, and wherein the left and right lateral sections **34iL**, **34iR** of a given module **34i** of the external ultrasound generating treating device **12** have ultrasonic imaging transducers **42iL**, **42iR** for forming respectively a

left and a right image of an emission zone of the treatment transducer or set of treatment transducers **20iL**, **20iR** held on the same section. With such a device, there is a direct and fixed correlation between the orientation of the emission and zone and the orientation of the imaging axis held by a same section. Therefore, superposition of the left and right emission zones can be achieved simply by adjusting the relative spatial configuration of the left and right sections **34iL**, **34iR** of the module **34i**, and by comparing the left and right images until a predefined correlation between the two images is obtained, which, by construction of the device, will be known to correspond to a superposition of the emission zones on a desired target location, e.g. on the spinal canal.

For example it is possible to construct the apparatus so that, when the spinal canal appears in the center of each left and right image, then the practitioner knows that the left and right emission zones are at least partially superposed on the treatment zone of the spinal cord or of the spinal nerves.

In a method as above, the treatment zone may extend throughout the extension of several vertebrae of the patient. This is most conveniently implemented with an external device as described above wherein the support structure **32** comprises several modules **34i** arranged successively along the longitudinal direction, the external device being positioned so that its longitudinal direction is parallel to the extension of the spine of the patient.

The method comprises the application to the treatment zone of the spinal cord and/or spinal nerves of the patient of at least one ultrasound treatment beam. This can be achieved by proper activation of the treatment transducer or set of treatment transducers **20iL**, **20iR** of an external device **12** as described above. The use of such a device allows for a very precise control of the ultrasound energy and power delivered to the targeted spinal cord and spinal nerve tissues. It also allows a precise targeting of the treatment zone, with the possibility to precisely control the extension of such treatment zone where the ultrasound treatment beam is effectively applied.

The terms "ultrasound beam", "ultrasound wave" and "ultrasound" are used indifferently for designating sound waves with frequencies higher than 20 kHz. However the ultrasound treatment beam has preferably an ultrasound frequency ranging from 0.5 to 4 MHz, more preferably ranging 0.75 to 2 MHz.

The method preferably involves the injection of an ultrasound contrast agent in the patient's blood circulation system, prior to and/or during the generation of the least one ultrasound treatment beam.

The term "ultrasound contrast agent" is used herein to refer to a substance (solid, liquid or gas) that is able to enhance the contrast between the region containing the agent and the surrounding tissue in an ultrasound image. Advantageously, the ultrasound contrast agent corresponds to small bubbles of a gas, termed "microbubbles," with an average diameter between 1 µm and 10µm. Said microbubbles oscillate and vibrate when a treatment ultrasound beam is applied and may reflect ultrasound waves. The ultrasound contrast agent is generally injected intravenously into the blood stream in the patient's blood circulation system, wherein it remains for a limited period of time.

The ultrasound contrast agent may be administered by injection, preferably by systemic injection. Examples of systemic injections include intravenous, subcutaneous, intramuscular, intradermal, intra vitreal and intraperitoneal injection, or perfusion.

Preferably, the ultrasound contrast agent is administered as a bolus just before the ultrasound treatment beam application. More preferably, the ultrasound contrast agent is administered between 0 and 60 minutes before, and/or during the ultrasound treatment beam application. When successive ultrasound treatment beams are applied, the ultrasound contrast agent is preferably delivered only once, just before the first ultrasound treatment beam application of the cycle, though it may be delivered at activation of each US beam, or by a continuous infusion through the activation of successive ultrasound treatment beams.

According to the invention, the ultrasound contrast agent may contain gaseous bubbles, a high concentration of gas, solid particles configured to vaporize in response to ultrasound, liquid configured to vaporize in response to ultrasound, micro particles configured to act as cavitation sites, solid particles having higher acoustic impedance than tissue in the desired region, and/or liquid with a high acoustic absorption coefficient.

In some embodiments, the ultrasound contrast agent is a microbubble contrast agent, preferably selected from the group consisting of sulphur hexafluoride microbubbles (SonoVue®), microbubbles made of an albumin shell and octafluoropropane gas core (Optison®), perflexane microbubbles encapsulated in an outer lipid shell (Imagent®), microbubbles made of octafluoropropane gas core encapsulated in an outer lipid shell (Definity®), or perfluorobutaine and nitrogen gas encapsulated in a lipid shell (BR38 – Schneider et al., 2011). Preferably, the ultrasound contrast agent consists of sulphur hexafluoride microbubbles. Microbubbles may contain a drug and/or a nanoparticle which may be delivered in situ when the microbubbles are exposed to the ultrasound treatment beam.

The microbubbles may have a mean diameter in a range from 1 μm to 10μm. In some embodiments, the microbubbles have a mean diameter in a range from 4 μm to 5 μm. In some other embodiments, the microbubbles have a mean diameter in a range from 2 to 6 μm. In some embodiments, the microbubbles have a mean diameter of approximately 7 μm, 6 μm, 5μm, 4μm, 3μm or 2μm. In a particular embodiment, the microbubbles have a mean diameter of approximately 2.5 μm.

In some embodiments, the dose of ultrasound contrast agent ranges between 0.05 and 0.15 ml/kg based on the total weight of the subject. Preferably, the dose of ultrasound contrast agent is approximately 0.1 ml/kg. In a particular embodiment, the maximum dose of ultrasound contrast agent is up to 10 ml.

Preferably, the pressure level of the ultrasound treatment beam applied to the spinal cord or spinal nerve tissues is comprised between 0.8 MPa and

3.0 MPa. Advantageously, the ultrasound treatment beams are applied within a pressure range of 0.8 MPa to 2.5 MPa, more preferably within a pressure range of 0.8 MPa to 2.00, even more preferably within a pressure range of 0.8 MPa to 1.9, such as within a pressure range of 0.8 MPa to 1.5 MPa, within a pressure range of 1.1 MPa to 1.5 MPa. In a particular embodiment, the ultrasound treatment beams are applied with a pressure level of 1.25 MPa. In another embodiment, the ultrasound treatment beams are applied with a pressure level of 1.5 MPa. In a further embodiment, the ultrasound treatment beams are applied with a pressure level of 1.9 MPa. In the context of the invention, the "pressure level" refers to the maximum acoustic pressure measured in the acoustic field of the device in water. It is believed that such pressure levels may be applied in a safe manner to human's spinal cord and/or spinal nerve, i.e., no detected damages of spinal cord and/or spinal nerve tissue should be observed.

In the context of the invention, the value of the pressure level corresponds to the value onto the spinal cord and/or spinal nerve tissue. The pressure emitted by the device may differ, to take into account potential attenuation of intervening tissues and/or vertebra bone reverberation. One skilled in the art will be able to adapt the value of the pressure level coming out of the emitter to obtain the required pressure level onto the spinal cord and/or spinal nerve. Monitoring of the treatment zone with ultrasonic monitoring transducers can be used for checking the effective value of the pressure level in situ during the treatment.

Preferably, the applied ultrasound treatment beam to the spinal cord or spinal nerve tissues has a mechanical index (MI) of approximately from 1 to 3.00, and preferably in the range of 1.05 to 1.8 in the case of a 1MHz ultrasound treatment beam. In the context of the invention, the MI refers to the peak negative pressure in situ (MPa) divided by the square root of the frequency (MHz).

Preferably, the ultrasound treatment beam is a pulsed beam. In the context of the invention, a "pulse" refers to a continuous burst, without interruption, of sinusoidal waves that may comprises several cycles.

In some embodiments, the method comprises the application one or more pulses, or bursts, comprising from 100 to 100,000 successive cycles, preferably from 1,000 to 75,000, more preferably from 10,000 to 50,000, even more preferably from 20,000 to 30,000. In a particular embodiment, the method comprises the application of pulses of 25,000 successive cycles. In some embodiments, the mean burst duration of an ultrasound treatment emission (i.e., the mean time from the start of a pulse to the end of that pulse) is between 10 msec. and 100 msec., preferably between 15 msec. and 50 msec., more preferably between 20 msec. and 30 msec., even more preferably approximately 25 msec.

The delay between two successive pulses is preferably from 30 msec. to 1000 msec. In a particular embodiment, the delay between two successive pulses is approximately 975 msec.

Advantageously, the successive pulses are applied within a total duration from 1 to 20 minutes. In a particular embodiment, the successive pulses are applied within a total duration that does not exceed 10 minutes, preferably 5 minutes. In a particular embodiment, the successive pulses are applied within a total duration of 150 seconds.

In a particular embodiment, pulses of 25,000 cycles are applied to the subject, at a pulse repetition frequency (PRF) of 1 Hz, every 1000 msec. with a pressure level of 1.1 MPa and a burst duration of about 23 msec. for a total duration of 150 seconds.

CLAIMS

1 - External ultrasound generating treating device (**12**) to induce spinal cord and/or spinal nerve treatment by emission of ultrasound waves, wherein the ultrasound generating treating device (**12**) is suitable for external positioning against the back of a patient, said device comprising an array of several ultrasound generating treatment transducers (**20iL, 20iR**) distributed along a longitudinal direction and a lateral direction, wherein the external ultrasound generating device comprises at least two sub-arrays of ultrasound generating treatment transducers, a left sub-array (**20iL**) being located on a left lateral side of a central longitudinal axis (**Ai**) and a right sub-array (**20iR**) being located on a right lateral side of the central longitudinal axis (**Ai**), laterally opposite to the left side,
characterized in that the device comprises a support structure (**32**) having at least one module (**34i**) comprising a left lateral section (**34iL**) holding at least a first left treatment transducer or set of treatment transducers of the left sub-array, and a right lateral section (**34iR**) holding at least a first right treatment transducer or set of treatment transducers of the right sub-array, and in that the support structure (**32**) maintains, in use of the device, a constant distance and a constant relative angular orientation around a longitudinal axis (**Ai**) between the first left and first right treatment transducers or set of treatment transducers (**20iL, 20iR**).

2 - External device according to claim 1, characterized in that the support structure comprises an adjusting mechanism (**36i**) for adjusting, around a longitudinal axis (**Ai**), a relative angular orientation between the left and right lateral sections (**34iL, 34iR**) of the support structure, so as to adjust the relative angular orientation around the longitudinal axis between the first left and first right treatment transducers or set of treatment transducers (**20iL, 20iR**).

3 - External device according to claim 2, characterized in that the adjusting mechanism (**36i**) comprises an articulation.

4 - External device according to any of claims 1 to 3, characterized in that the support structure comprises an adjusting mechanism (**36i**) for adjusting

a distance between the left and right lateral sections of the support structure (**34iL, 34iR**), so as to adjust the distance between the first left and first right treatment transducers or set of treatment transducers (**20iL, 20iR**).

5 - External device according to claim 4, characterized in that the adjusting mechanism comprises a lock (**40i**) for maintaining, in use of the device, a constant distance and a constant relative angular orientation around the central longitudinal axis between the first left and first right treatment transducers or set of treatment transducers (**20iL, 20iR**).

6 - External device according to any preceding claim, characterized in that the left and right lateral sections (**34iL, 34iR**) have ultrasonic imaging transducers (**42iL, 42iR**) for forming respectively a left and a right image of an emission zone of the treatment transducer or set of treatment transducers (**20iL, 20iR**) held on the same section (**34iL, 34iR**).

7 - External device according to any preceding claim, characterized in that the external ultrasound generating treating device comprises ultrasonic monitoring transducers (**44iL, 44iR**).

8 - External device according to any preceding claim, characterized in that the support structure (**32**) comprises several modules (**34i**) arranged successively along the longitudinal direction, each module comprising a left lateral section (**34iL**), holding at least a left treatment transducer or set of treatment transducers (**20iL**) of the left sub-array, and a right lateral section (**34iR**), holding at least a right treatment transducer or set of treatment transducers (**20iR**) of the right sub-array, and in that the support structure (**32**) maintains, in use of the device, a constant distance and a constant relative angular orientation around a longitudinal axis between the respective left and right treatment transducers or set of treatment transducers (**20iL, 20iR**).

9 - External device according to claim 8, characterized in that several modules (**34i**) have each an adjusting mechanism (**36i**) for adjusting, around a longitudinal axis, a relative angular orientation between the respective left and right lateral sections of the support structure (**34iL, 34iR**), so as to adjust the angular orientation around a longitudinal axis

between the first left and first right treatment transducers or set of treatment transducers (**20iL, 20iR**).

10 - External device according to any claim 9, characterized in that the adjusting mechanisms (**36i**) of several modules (**34i**) are mechanically connected for simultaneous adjustment.

11 - External device according to any of claim 8 to 10, characterized in that at least two modules (**34i**) of the support structure (**32**) are articulated (**46**) to allow a relative angular movement between the two modules (**34i**) around an axis extending along the lateral direction.

12 - External device according to claim 11, characterized in that the at least two modules (**34i**) of the support structure are articulated through a flexible module connector (**46**).

13 - Apparatus for inducing spinal cord and/or spinal nerve treatment by emission of ultrasound waves, characterized in that it comprises:

- an external ultrasound generating treating device (**12**) according to any preceding claim;
- a generator (**10**) to supply electricity to the external ultrasound generating treating device;
- a controller (**15**).

14 - Apparatus according to claim 13 in combination with claim 6, characterized in that the left and right lateral sections (**34iL, 34iR**) of the external ultrasound generating treating device (**12**) have ultrasonic imaging transducers (**42iL, 42iR**) for forming respectively a left and a right image of an emission zone of the treatment transducer or set of treatment transducers (**20iL, 20iR**) held on the same section (**34iL, 34iR**), and in that the controller (**15**) comprises an imaging module (**15B**) connected to the imaging transducers.

15 - Method for transiently opening the blood-spinal cord barrier and/or the blood spinal nerves barrier in at least one treatment zone of the spinal cord and/or spinal nerves of a patient, said method comprising :

- positioning externally against the back of the patient:

- at least one left ultrasound generating treatment transducer or set of treatment transducers (**20iL**), having a left emission zone, on a left lateral side of the back of the patient with respect to the spine of the patient, and
- at least one right ultrasound generating treatment transducer or set of treatment transducers (**20iR**), having a right emission zone, on a right lateral side of the back of the patient with respect to the spine of the patient,

- forming at least one left image along a left imaging axis having a set orientation with respect to the left emission zone and one right image along right imaging axis having a set orientation with respect to the right emission zone;
- orienting the left and right emission zones according to the left and right images so that the left and right ultrasound emission zones are at least partially superposed on the treatment zone of the spinal cord or on the spinal nerves.

16 - Method according to claim 15, wherein orienting the left and right emission comprises orienting the treatment transducers or set of treatment transducers (**20iL, 20iR**) according to the left and right images so that the left and right ultrasound emission zones are at least partially superposed on the treatment zone of the spinal cord or on the spinal nerves.

17 - Method according to claim 15, wherein orienting the left and right emission comprises controlling the left and a right treatment transducers or set of treatment transducers (**20iL, 20iR**) so as to electronically steer the left and right emission zones.

18 - Method according to any of claims 15 to 17, wherein the treatment zone extends throughout the extension of several vertebrae of the patient.

19 - Method according to any of claims 15 to 18, wherein the method involves the intravenous injection of an ultrasound contrast agent in the patient's blood circulation system, prior to and/or during the generation of the least one ultrasound treatment beam.

20 - Method according to any of claims 15 to 19, wherein the treatment ultrasound beam has a resonant frequency ranging from 0.5 to 4 MHz.

21 - Method according to any of claims 15 to 20, wherein the pressure level of the treatment beam is calculated to obtain a pressure level within the spinal cord and/or spinal nerve tissues between 0.8 MPa and 3.0 MPa.

22 - Method according to any of claims 15 to 21, wherein the applied treatment beam is determined to obtain a mechanical index (MI) within the spinal cord and/or spinal nerve tissues of from 0.3 to 3.0.

23 - Method according to any of claim 15 to 22, wherein the method is implemented with an external ultrasound generating treating device (**12**) conform to any of claims 1 to 12.

24 - Method according to any of claim 15 to 23, wherein the method is used to treat at least one of ;

- a spinal degenerative pathology, such as amyotrophic lateral sclerosis (ALS);
- a spinal cord tumor disease, such as spinal astrocytomas ;
- a spinal inflammatory pathology, such as multiple sclerosis;

or to improve the repair and/or rehabilitation treatments of the spinal cord and/or spinal nerve(s), including with cell transplant and/or stem cell regeneration.

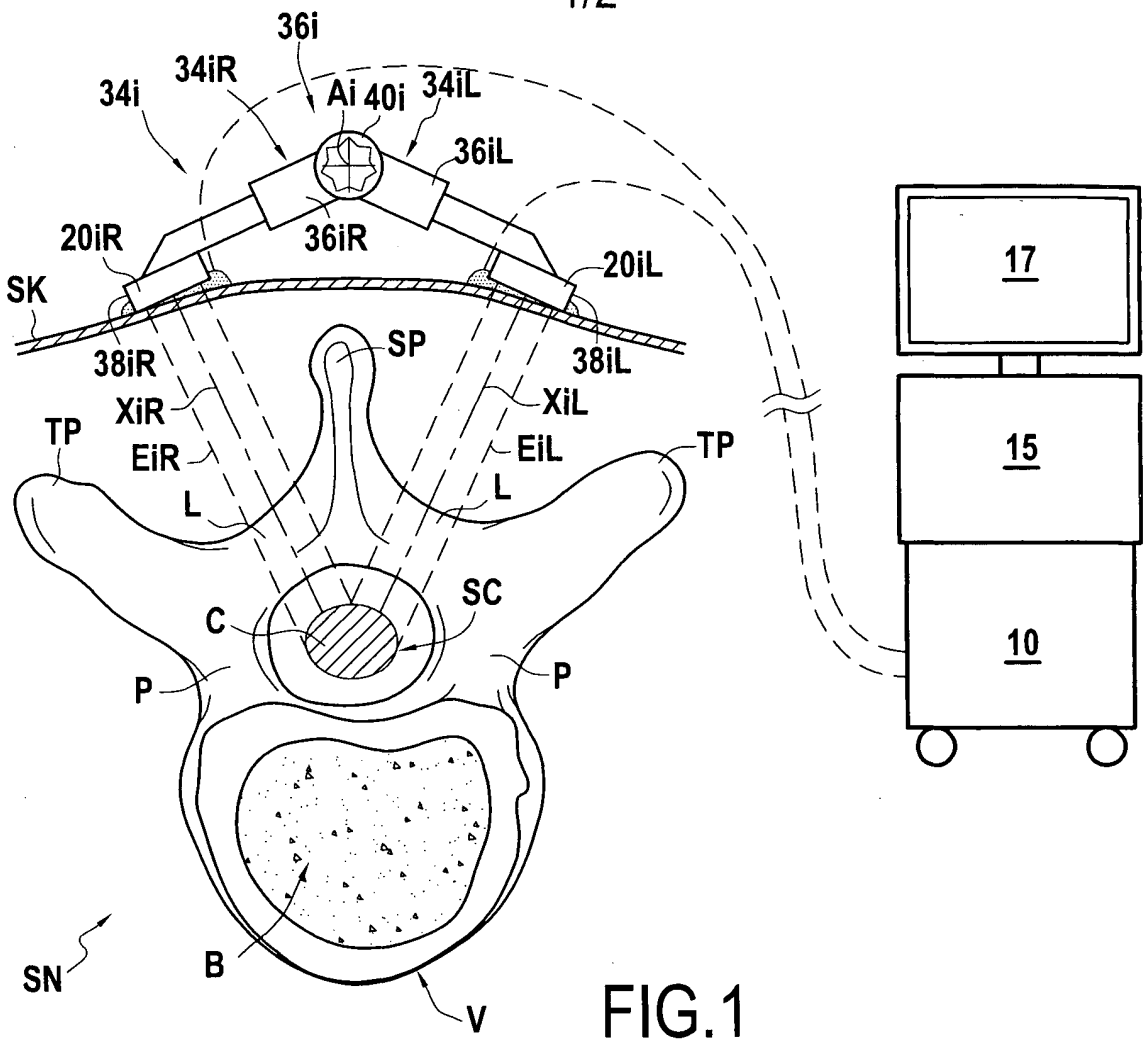
36i
34iR
34i
Ai 40i
34iL
36iL
20iR
36iR
20iL
SK
38iR
SP
38iL
XiR
XiL
TP
EiR
EiL
TP
L
L
SC
C
P
P
17
15
10
SN
B
V

FIG.1

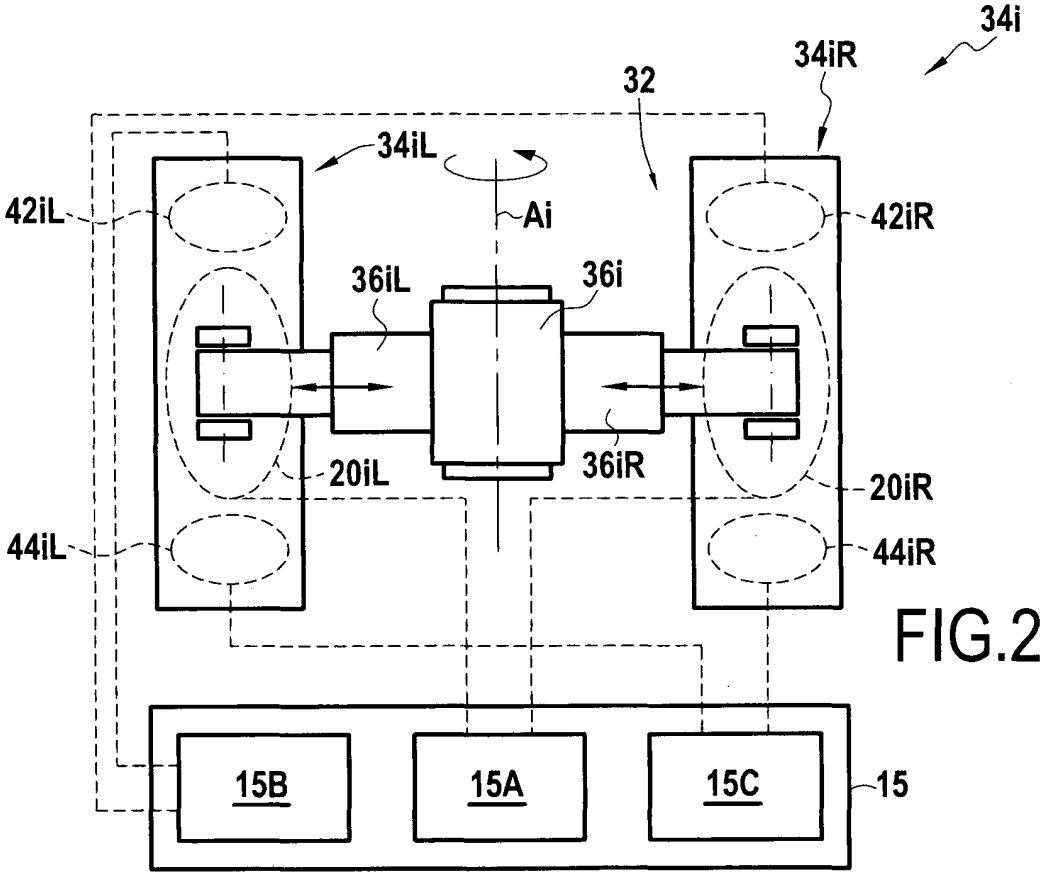
34i
34iR
32
34iL
Ai
42iL
42iR
36iL
36i
20iL
36iR
20iR
44iL
44iR
15B
15A
15C
15

FIG.2

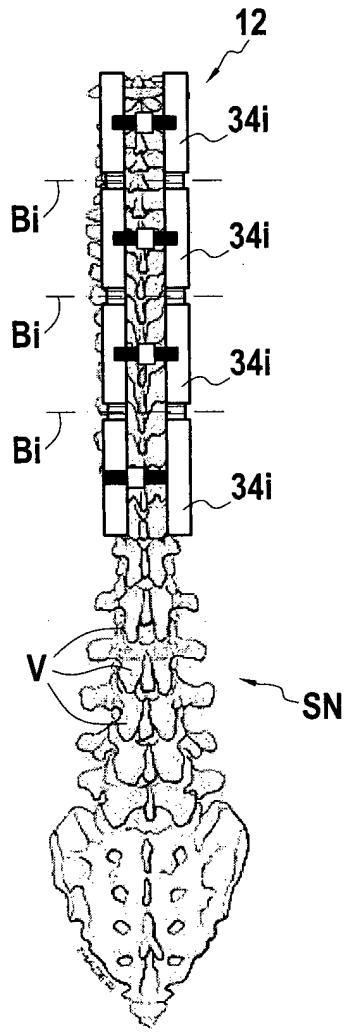

FIG.3

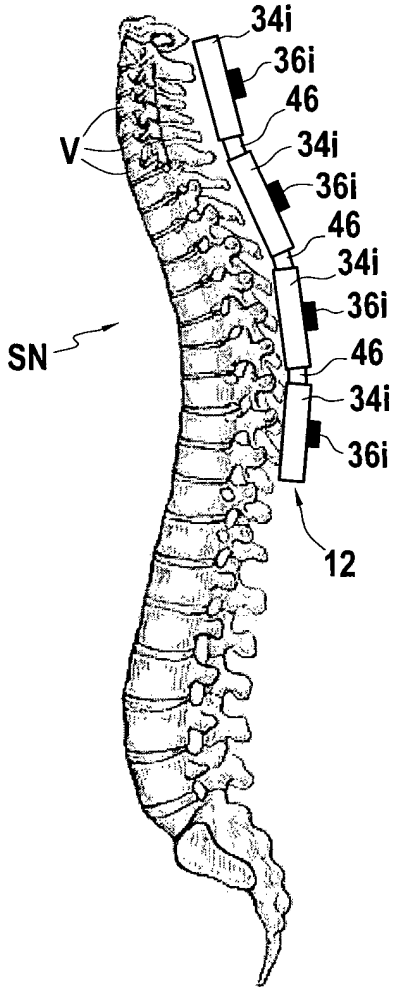

FIG.4

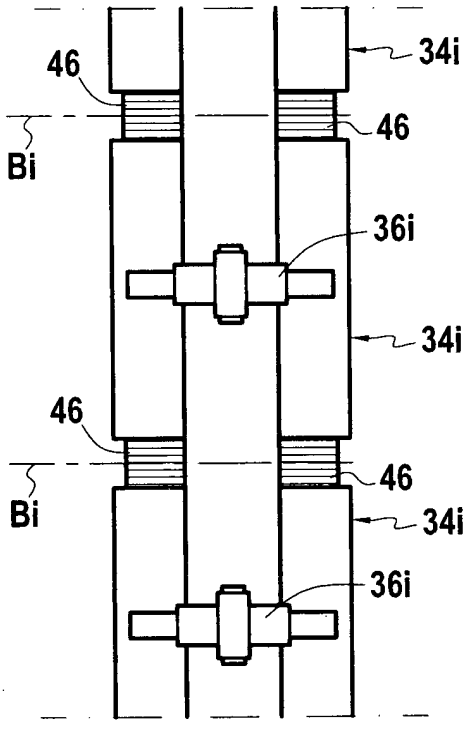

FIG.5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/000431

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B8/00 A61N7/00
ADD.

According to International Patent Classification (IPC) or to both national classifioation and IPC

B. FIELDS SEARCHED

Minimum documentation searched (olassification system followed by classification symbols)
A61N A61M A61B

Documentation searched other than minimum dooumentation to the extent that suoh documents are inoluded in the fields searched

Electronic data base consulted during the international searoh (name of data base and, where praoticable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of dooument, with indioation, where appropriate, of the relevant passages	Relevant to olaim No.
X Y	US 2016/016012 A1 (YOUN INCHAN [KR] ET AL) 21 January 2016 (2016-01-21) cited in the application paragraphs [0019], [0037], [0039] - [0045], [0077] figures 1-4	1,7,13 6,8,11, 12,14

X Y	US 4 836 191 A (NOSKE ERICH [DE] ET AL) 6 June 1989 (1989-06-06) the whole document	1-5,7,13 6,8-12, 14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier applioation or patent but published on or after the international filing date

"L" dooument which may throw doubts on priority olaim(s) or which is cited to establish the publioation date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" dooument published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but oited to understand the prinoiple or theory underlying the invention

"X" dooument of particular relevanoe; the claimed invention oannot be considered novel or cannot be oonsidered to involve an inventive step when the document is taken alone

"Y" dooument of particular relevanoe; the claimed invention oannot be considered to involve an inventive step when the document is combined with one or more other such doouments, such combination being obvious to a person skilled in the art

"&" dooument member of the same patent family

Date of the aotual completion of the international searoh	Date of mailing of the international searoh report
27 October 2016	03/11/2016

Name and mailing address of the ISA/	Authorized offioer
European Patent Offioe, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rosander, Frida

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/000431

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of dooument, with indioation, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/000431

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15-24
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful internaticnal search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 15-24

Claims 15-24 refer to a method for treatment of the human or animal body by therapy, since they relate to a method for opening the blood-spinal cord barrier and/or the blood spinal nerves barrier in order to i.a. allow therapeutic substances to be delivered into the spinal cord or spinal nerve tissue, as disclosed by the description e.g. pages 1 and 25-27. Furthermore, claims 15-24 additionally refers to a method for treatment of the human or animal body by surgery, as both the opening of the blood-spinal cord barrier and/or the blood spinal nerves barrier and the intravenous injection of an ultrasound contrast agent, see claim 19, are considered to involve substantial health risks even when carried out with required medical professional skills. According to Rule 39.1(iv) PCT, a search is not required to be carried out for these claims.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/000431

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		WO 0078232 A1	28-12-2000

专利名称(译)	用于脊髓和脊神经治疗的外部超声波产生治疗装置，包括这种装置的装置和实施这种装置的方法		
公开(公告)号	EP3426157A1	公开(公告)日	2019-01-16
申请号	EP2016719897	申请日	2016-03-11
申请(专利权)人(译)	援助PUBLIQUE - HÔPITAUXDE PARIS		
当前申请(专利权)人(译)	援助PUBLIQUE - HÔPITAUXDE PARIS		
[标]发明人	CARPENTIER ALEXANDRE		
发明人	CARPENTIER, ALEXANDRE		
IPC分类号	A61B8/00 A61N7/00		
CPC分类号	A61B8/0875 A61B8/4477 A61B8/481 A61N7/00 A61N2007/0026 A61N2007/0078 A61N2007/0091		
外部链接	Espacenet		

摘要(译)

本发明涉及一种外部超声波发生治疗装置（12），用于诱导脊髓和/或脊神经治疗，包括至少两个超声波产生治疗换能器子阵列，左子阵列（20iL）位于左侧面和右侧子阵列（20iR）位于中心纵向轴线（Ai）的右侧面上，其特征在于，该装置包括具有至少一个模块（34i）的支撑结构（32），该模块包括左侧横截面（34iL）和右侧横截面（34iR），并且支撑结构（32）在使用该装置时保持恒定距离和围绕中心纵向轴线（Ai）的恒定相对角度取向。第一左和右第一治疗换能器或一组治疗换能器（20iL，20iR）。本发明还提供了一种包括这种装置和方法的装置。