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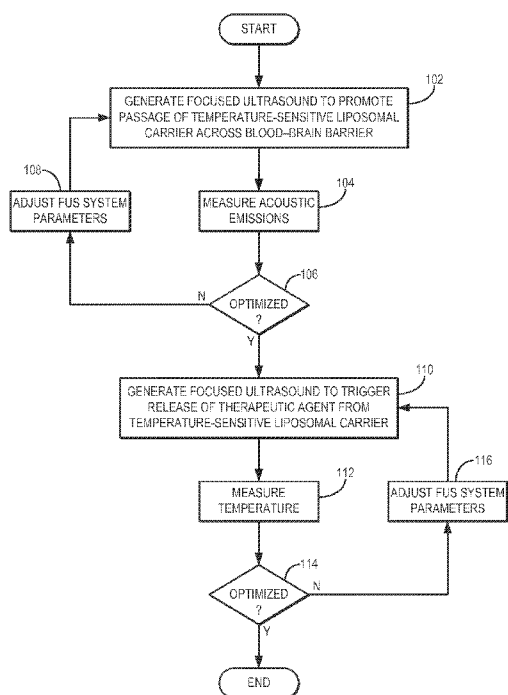


FIG. 1

(57) Abstract: Systems and methods are described for using focused ultrasound to promote the delivery of a temperature-sensitive liposomal carrier containing a therapeutic agent across the blood-brain barrier ("BBB"), where the temperature-sensitive liposomal carrier is then triggered to release the therapeutic agent using focused ultrasound. An advantage of the systems and methods described here is the ability to improve delivery of the therapeutic agent to a tissue-of-interest (e.g., tumor cells, such as those in a brain tumor) while minimizing the systemic dose.

**SYSTEMS AND METHODS FOR CONTROLLING FOCUSED ULTRASOUND TO TARGET
RELEASE OF A THERAPEUTIC AGENT FROM TEMPERATURE-SENSITIVE
LIPOSOMAL CARRIERS**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 62/017,498, filed on June 26, 2014, and entitled "FOCUSED ULTRASOUND TARGETED DRUG DELIVERY."

BACKGROUND OF THE INVENTION

[0002] The field of the invention is systems and methods for focused ultrasound. More particularly, the invention relates to systems and methods for controlling focused ultrasound to trigger the delivery and release of a therapeutic agent.

[0003] Focused ultrasound ("FUS") is a promising technology that has shown exciting potential for treatment of brain disorders. To date, transcranial FUS has been used for non-invasive surgery for chronic pain, essential tremor, and glioblastoma. These investigations have been based on the thermal ablation of targeted brain tissue using FUS, and have been guided by magnetic resonance imaging ("MRI"), in which MRI thermometry is used to measure temperature elevations during treatment.

[0004] There are also non-thermal, cavitation-mediated applications of FUS that are being investigated pre-clinically, such as transient opening of the blood-brain barrier ("BBB") for targeted drug delivery or sonothrombolysis for the treatment of ischemic stroke.

[0005] The treatment of patients with brain tumors such as malignant glioma remains a major medical problem. But, research in animals has shown that FUS with microbubbles can transiently disrupt the blood-brain barrier ("BBB"), including the irregular blood-tumor barrier ("BTB"), offering a completely noninvasive approach to

improve drug uptake. This technique provides hope for chemotherapy agents, such as doxorubicin, to be cytotoxic in brain tumors if effectively delivered to the tumor and surrounding tissue. Further, chemotherapy encapsulation using stealth liposomes can increase drug circulation times and intratumoral delivery while reducing systemic side effects. However, despite FUS-induced BBB/BBB disruption, encapsulation limits the uptake of chemotherapy or other therapeutic agents to only the tumor periphery, and results in poor penetration and low cytotoxic payload to cancer cells.

[0006] Malignant gliomas are often infiltrative, which prevents their total resection and results in high incidence of recurrence. Treatments with intravenously administered chemotherapeutic drugs that can potentially reach infiltrating cells have limited use because of adverse systemic effects associated with nonspecific delivery and poor extravasation across the BBB. Active efflux of the drugs back to the circulation also significantly limits their cytotoxicity.

[0007] Thus, there remains a need to provide systems and methods for highly targeted delivery of therapeutic agents to a tissue-of-interest, such as a tumor, that are capable of non-invasively delivering the therapeutic agent both deep within the tissue and surrounding infiltrations.

SUMMARY OF THE INVENTION

[0008] The present invention overcomes the aforementioned drawbacks by providing a method for using a focused ultrasound system to effectuate a treatment of a tissue in a subject who has been administered a temperature-sensitive liposomal carrier containing a therapeutic agent. A first focused ultrasound energy is produced in a target region, wherein the first focused ultrasound energy is sufficient to promote passage of the temperature-sensitive liposomal carrier containing the therapeutic agent across a

blood-brain barrier. A second focused ultrasound energy is then produced in the target region after the first focused ultrasound energy has been produced. The second focused ultrasound energy is sufficient to alter a temperature in the target region so as to trigger release of the therapeutic agent from the temperature-sensitive liposomal carrier. Release of the therapeutic agent effectuates treatment of the tissue in the target region.

[0009] It is an aspect of the invention that acoustic emissions from microbubble oscillations, which may include cavitation, can be measured and that the first focused ultrasound energy can be adjusted based on the acoustic emissions. Measuring the acoustic emissions can include passively recording the acoustic emissions, and can also include producing a cavitation map that depicts a type (e.g., stable or inertial), strength and a location of cavitation event. Such a cavitation map can be produced based on a backprojection of the acoustic emissions.

[0010] It is another aspect of the invention that measuring the acoustic emissions can include producing a quantitative measurement of the acoustic emissions based in part on a numerical simulation that accounts for propagation characteristics of acoustic waves emitted by oscillating microbubbles.

[0011] It is another aspect of the invention that the temperature in the target region can be measured and that the second focused ultrasound energy can be adjusted to increase the temperature in the target region to within an effective temperature range. In some embodiments, the effective temperature range is from about 38 degrees Celsius to about 45 degrees Celsius. In some other embodiments, the effective temperature range is from about 40 degrees Celsius to about 42 degrees Celsius.

[0012] It is still another aspect of the invention to provide a focused ultrasound system for use in promoting delivery of a temperature-sensitive liposomal carrier containing a therapeutic agent to a tissue in a subject. The focused ultrasound system

generally includes a transducer configured to generate focused ultrasound energy, and a controller in communication with the transducer. The controller is programmed to control the transducer to produce first focused ultrasound energy in a target region, wherein the first focused ultrasound energy is sufficient to promote passage of the temperature-sensitive liposomal carrier containing the therapeutic agent across a blood-brain barrier. The controller is also programmed to control the transducer to produce second focused ultrasound energy in the target region, wherein the second focused ultrasound energy is sufficient to alter a temperature in the target region so as to trigger release of the therapeutic agent from the temperature-sensitive liposomal carrier.

[0013] It is an aspect of the invention that the focused ultrasound system can include another transducer, or array of transducers, in communication with the controller that is configured to generate ultrasound energy, and wherein the transducer and the another transducer are confocally aligned with the target region.

[0014] It is another aspect of the invention that the focused ultrasound system can include another transducer, or array of transducers, in communication with the controller that is configured to passively measure acoustic emissions from the target region, and wherein the transducer and the another transducer are confocally aligned with the target region.

[0015] The foregoing and other aspects and advantages of the invention will appear from the following description. In the description, reference is made to the accompanying drawings that form a part hereof, and in which there is shown by way of illustration a preferred embodiment of the invention. Such embodiment does not necessarily represent the full scope of the invention, however, and reference is made therefore to the claims and herein for interpreting the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 is a flowchart setting forth the steps of an example method for using focused ultrasound to effectuate treatment with a therapeutic agent delivered to a tissue-of-interest using a temperature-sensitive liposomal carrier;

[0017] FIG. 2 is an example plot illustrating the use of acoustic emissions in the process of predicting or otherwise modulating the promotion of BBB opening;

[0018] FIG. 3 is an example of a cavitation map produced from acoustic emissions measured from oscillations of a microbubble agent and demonstrates the use of the peak intensity of the map to control the focal pressure for safe and effective promotion of BBB opening;

[0019] FIG. 4 is an example plot illustrating the use of focused ultrasound energy to maintain an effective temperature in the target region for a duration sufficient to effectuate release of a therapeutic agent from a temperature-sensitive liposomal carrier;

[0020] FIG. 5 is a pulse timing diagram showing an example timing for generating the first and second focused ultrasound energies to promote opening of the blood-brain barrier and to trigger release of a therapeutic agent from a temperature-sensitive liposomal carrier, respectively;

[0021] FIG. 6 is a block diagram of an example focused ultrasound system that can implement the present invention;

[0022] FIG. 7 is an illustration showing two confocal focused ultrasound transducers and a linear array ultrasound transducer that is also confocal with the focused ultrasound transducers, and where the beam axis of each transducer is orthogonal to the others; and

[0023] FIG. 8 is an illustration showing a focused ultrasound transducer having an aperture through which a conventional ultrasound transducer can be provided, such

that the focused ultrasound transducer and the conventional ultrasound transducer are confocally aligned.

DETAILED DESCRIPTION OF THE INVENTION

[0024] Described here are systems and methods for using focused ultrasound to promote the delivery of a temperature-sensitive liposomal carrier containing a therapeutic agent across the blood-brain barrier ("BBB"), where the temperature-sensitive liposomal carrier is then triggered to release the therapeutic agent using focused ultrasound. An advantage of the systems and methods described here is the ability to optimize delivery of the therapeutic agent to a tissue-of-interest (e.g., tumor cells, such as those in a brain tumor) while minimizing the systemic dose.

[0025] The temperature-sensitive liposomal carrier can include a low-temperature-sensitive ("LTS") liposome. As used here in relation to the temperature-sensitive liposome, the term "low-temperature" generally refers to temperatures at or above normal body temperature (e.g., about 37°C to about 50°C). In some embodiments, the temperature-sensitive liposomal carrier can be a temperature-sensitive functionalized liposomal carrier. As one example, the functionalized liposomal carrier can be a targeted liposomal carrier that includes a targeting moiety having specificity for a particular tissue type, such as tumor cells. Targeted liposomal carriers can include antibody conjugated liposomal carriers, in which the targeting moiety can either be a polyclonal or monoclonal antibody conjugated with the liposomal carrier. As one example, an antibody conjugated liposomal carrier can be conjugated with anti-transferrin monoclonal antibodies ("OX26-mAb"). Glioma cells and brain capillaries are known to over-express transferrin receptor; thus, the particular labeling of the temperature-sensitive liposomal carrier with OX26-mAb can significantly improve the

transport of therapeutic agents from blood into the brain endothelium and eventually into the tumor cells.

[0026] Increasing the temperature in the environment local to the temperature-sensitive liposomal carrier results in localized release of the liposomal cargo (i.e., the therapeutic agent). The therapeutic agent can generally include chemotherapy agents. As one specific example, the therapeutic agent can be doxorubicin. Thus, as one specific, non-limiting example, the temperature-sensitive liposomal carrier can include LTS-liposomes containing doxorubicin, such as those available under the trade name ThermoDox® (Celsion Corp.; Lawrenceville, New Jersey).

[0027] As will be described below in detail, focused ultrasound can be used to increase the temperature in a focal region in a controlled manner that does not generate adverse effects to the patient (e.g., excess heating in the skull or tissue). In this manner, the temperature-sensitive liposomal carrier can be triggered with focused ultrasound to release the encapsulated therapeutic agent in a highly localized region. Accordingly, delivery of the therapeutic agent can be optimized to the tissue-of-interest (e.g., tumor cells) while minimizing systemic and non-specific dose.

[0028] The systems and methods described here generally implement a first focused ultrasound energy to promote passage of a temperature-sensitive liposomal carrier across the blood-brain barrier. This first focused ultrasound energy preconditions the targeted region in order to promote the unobstructed transport of otherwise restricted transport of the liposomal carriers and their cargo.

[0029] In general, the therapeutic agents have limited effectiveness because the therapeutic agents are generally unable to penetrate beyond the perivascular space. It is contemplated that this poor penetration is due to factors associated with dense tumor collagen matrix, high interstitial pressure, poor diffusion of the liposomal carrier due to

its large size (e.g., 100 nm), the restricted permeability of the BBB for targets in the brain, or combinations of these factors.

[0030] A second focused ultrasound energy is utilized to increase the temperature in a focal region when release of a therapeutic agent that is contained in a temperature-sensitive liposomal carrier is triggered. By releasing the therapeutic agent from the liposomal carrier using the second focused ultrasound energy, the probability of complete therapeutic agent secretion within the sonicated region can be significantly increased. This temperature increase can also increase local blood flow, which can lead to increased therapeutic agent concentrations and reduced hypoxia (potentially increasing efficacy of the therapeutic agent). In addition, therapeutic agents that are released in this manner within the vasculature of normal tissue and tumor vasculature can be delivered across vessels that are permeable, but not permeable enough to allow the intact liposomal carrier to cross. This feature of the systems and methods described here advantageously enables delivery of therapeutic agents to infiltrating cancer cells in brain regions surrounding a vascular tumor, where the BBB is intact.

[0031] Referring now to FIG. 1, a flowchart is illustrated as setting forth the steps of an example method for using focused ultrasound to effectuate treatment with a therapeutic agent delivered to a tissue-of-interest using a temperature-sensitive liposomal carrier.

[0032] The method includes controlling the operation of a focused ultrasound ("FUS") system to generate focused ultrasound energy sufficient to promote passage of a temperature-sensitive liposomal carrier across the blood-brain barrier ("BBB"), as indicated at step 102. In some embodiments, the blood-brain barrier can include a blood-tumor barrier. The promotion of the temperature-sensitive liposomal carrier's passage across the BBB is mediated, in part, by a microbubble agent that has been

previously administered to the subject. The focused ultrasound energy generated by the FUS system induces stable cavitation of the microbubbles in a manner that promotes opening of the BBB to the passage of the temperature-sensitive liposomal carrier.

[0033] Preferably, the operation of the FUS system is monitored to provide feedback to adjust control of the FUS system to optimize passage of the temperature-sensitive liposomal carrier across the BBB. To this end, acoustic emissions can be measured during the sonication with the first focused ultrasound energy, as indicated at step 104. For example, the strength of harmonic emissions originating from the oscillations of the microbubble agent can be monitored to assess the onset and degree to which the BBB is opened. FIG. 2 illustrates an example use of acoustic emissions measured from oscillations of a microbubble agent to predict or otherwise modulate the degree to which opening of the BBB is promoted by application of the first focused ultrasound energy. To this end, a feedback loop can be implemented, as indicated at decision block 106, to optimize the focused ultrasound for maximal promotion of the passage of the liposomal carrier across the BBB. Thus, the FUS system parameters are adjusted at step 108, as needed, when implementing the feedback loop.

[0034] In general, the focused ultrasound and its corresponding effect at promoting passage of the temperature-sensitive liposomal carrier can be monitored using passive ultrasonography techniques. As one example, the passive ultrasonography technique can include dynamically mapping acoustic emissions originating from microbubbles and, in some instances, assessing the spectral content of those acoustic emissions. In general, cavitation mapping relies on recording spatially coherent acoustic emissions using number of passive cavitation detectors. Based on these recorded data, cavitation activity can be localized in two or three dimensions. An example of a cavitation map and a plot of intensity values corresponding to the cavitation map, which

can be used to assess whether the first ultrasound energy should be adjusted, are illustrated in FIG. 3. The cavitation map and associated intensity plot can be analyzed to assess whether sufficient cavitation is occurring to promote opening of the BBB, or whether the first focused ultrasound energy being generated is too strong. Based on the analysis of this information, a determination can be made whether the first focused ultrasound energy should be appropriately adjusted.

[0035] As one example, the cavitation maps can be produced by passively measuring acoustic emissions from the microbubbles and using backprojection techniques to produce an image (i.e., the cavitation map) that depicts the location of the microbubbles. In this example, using confocal transducer arrays to measure the acoustic emissions, spatial samples of the pressure waves emitted from the microbubbles are synchronously collected. The collected data are then backprojected to the imaging plane to depict the origin and strength of the emitted pressure waves.

[0036] As one example, a fast planar projection method, such as an angular spectrum approach, for backprojecting the passively recorded diverging pressure wave can be used. This technique generally relates a field between two spatially separated planes, or lines, by a projection operator in the wavevector-frequency domain. The image amplitude reflects the intensity of the acoustic emissions at a given frequency. This algorithm can be readily extended to include multiple frequencies (e.g., harmonics, ultraharmonics, subharmonics, broadband). A major advantage of planar projection methods, such as the angular spectrum approach, is a substantial reduction in computation time as compared to integral finite element, finite difference, or cross-correlation time-domain approaches. These backprojection algorithms can also be readily extended to compensate for absorption, reflection, and aberration of the emitted pressure wave, thereby making it possible to extract quantitative information about the

microbubble distribution, even behind highly aberrating media such as the skull.

[0037] Spectral methods, such as the angular spectrum approach, allow the performance of frequency-selective passive cavitation mapping. Using such a technique, information about the location and type of acoustic cavitation can be extracted from the recorded acoustic emissions using appropriate frequency bands.

[0038] The power spectrum can also be measured from the recorded data. Therefore, frequency-domain analysis of the recorded acoustic emissions can be used to extract information about the type of acoustic cavitation.

[0039] Acoustic emissions in isolation are not quantitative because they depend on the location of the emission source with respect to the detector, in addition to the attenuation of the acoustic emission by the tissue and skull. To minimize receiver-related variability in the recorded acoustic emissions, the measured acoustic emissions can be processed to generate a quantitative acoustic emission map.

[0040] Quantifying the acoustic emissions requires estimating the fraction of the recorded signal from the original emissions. To achieve this quantification, passive ultrasonography can be combined with sound propagation models to take into account reflection, absorption, and dispersion of sound through the skull. Thus, in a preferred embodiment, a patient-specific numerical simulation is implemented to take into account the propagation of emitted acoustic waves in order to quantify passively recorded acoustic emissions. Quantifying acoustic emissions in this manner provides a quantitative estimation of the strength of the acoustic emissions. Also, in some embodiments, the quantitative acoustic emission map can be correlated with an estimate of the temperature-sensitive liposomal carrier's uptake into the tissue-of-interest as a way of monitoring or otherwise assessing the treatment.

[0041] After the temperature-sensitive liposomal carrier has passed across the

BBB, the FUS system is once again controlled to generate focused ultrasound energy; however, at this time the focused ultrasound energy that is generated is sufficient to trigger release of the therapeutic agent contained in the temperature-sensitive liposomal carrier, as indicated at step 110. An example plot illustrating a temperature control that can be achieved using focused ultrasound is shown in FIG. 4. The effective temperature range for the release of a therapeutic agent from its liposomal carrier is also shown as the region between the dotted and dashed lines.

[0042] In general, the focused ultrasound energy generated in step 110 is sufficient to maintain a temperature within a range of effective temperatures in the focal region. As one example, the range of effective temperatures can be about 38°C to about 45°C. As another example, the range of effective temperatures can be from about 40°C to about 42°C. It will be appreciated by those skilled in the art, however, that the range of effective temperatures, and the duration for which they should be maintained, may vary depending on the particular temperature-sensitive liposomal carrier. In some embodiments, where the tissue-of-interest is not beyond the BBB, the first sonication for promoting passage of the liposomal carrier across the BBB will not be necessary. In these applications, only the second sonication for triggering release of the therapeutic agent from the temperature-sensitive liposomal carrier would be necessary.

[0043] More generally, the effective temperature and the duration for which it should be maintained can be described based on a thermal dose limit. The thermal dose metric is typically reported in "equivalent minutes" at a reference temperature, which is often selected as 43°C. An example of calculating thermal dose is described by S.A. Sapareto and W.C. Dewey in "Thermal dose determination in cancer therapy," *International Journal of Radiation Oncology Biology Physics*, vol. 10, no. 6, pp. 787-800, 1984. Preferably, the effective temperature and duration at which that temperature is

maintained should not exceed a thermal dose of about 240 equivalent minutes at 43°C.

[0044] As one example, focused ultrasound energy sufficient to trigger release of the therapeutic agent from the temperature-sensitive liposomal carrier includes applying a sonication for a duration of 15 seconds. It is contemplated that longer durations of sonications may result in better results, as long as the thermal dose is maintained below 240 equivalent minutes, which is the thermal dose at which undesirable heating of the tissue or skull is likely to occur. Therefore, in some embodiments, a multiple beam path sonication scheme can be implemented to reduce undesirable heating of the skull.

[0045] To implement a multiple beam path sonication scheme, the FUS system preferably includes two, confocally aligned FUS transducers. Also, in some embodiments, pulsed sonications can be used to adjust the size of the focal region, thereby expanding the safety margin of the focused ultrasound delivery. Spherical sonication trajectories can also be implemented for heating larger volumes.

[0046] In some embodiments, the focused ultrasound energy generated in step 110 is sufficient to both trigger release of the therapeutic agent from the temperature-sensitive liposomal carrier and to provide FUS-induced thermal ablation in the focal region. In these embodiments, targeted delivery of the therapeutic agent is augmented by the resulting heat convection and diffusion from the targeted area.

[0047] The focused ultrasound energy used to trigger release of the therapeutic agent from the temperature-sensitive liposomal carrier can be monitored by measuring the temperature change in the focal region, as indicated at step 112. As one example, magnetic resonance thermometry techniques can be used to monitor the temperature changes associated with delivering the focused ultrasound energy to the target region. In general, the measured temperature information can be used in a feedback loop to

control the operation of the FUS system. To this end, a feedback loop can be implemented, as indicated at decision block 114. If the focused ultrasound is not achieving the desired temperature in the target region, then the FUS parameters can be adjusted at step 116, as needed. An example of magnetic resonance images produced using magnetic resonance thermometry techniques are illustrated in FIG. 4, along with an example plot of temperature increase in the region being monitored by the magnetic resonance thermometry. The information derived from these images can this be used to monitor the temperature rise in the target region, which can be used to assess whether an effective temperature or effective thermal dose is being achieved.

[0048] A list of example ultrasound parameters that can be used to promote opening of the BBB, such that the temperature-sensitive liposomal carrier can pass across the BBB, and to achieve and maintain the effective temperature increase in the target region is shown in Table 1 below. The events listed in Table 1 (promoting BBB opening, microbubble clearance, slow LTS-liposomal carrier infusion, and temperature increase) are referenced in the example pulse timing diagram illustrated in FIG. 5. In general, FIG. 5 illustrates an example pulse timing for the generation of the first focused ultrasound energy 40 and the second focused ultrasound energy 42. The pulse timing diagram also indicates an example time 44 at which a microbubble agent can be provided to the target region and an example time 46 at which the temperature-sensitive liposomal carrier can be provided to the target region.

Table 1

	Time (mins)	Duration (mins)	Focal Power (Watts)
Promoting BBB Opening	0-2	1-5	0.01-1.00
Microbubble Clearance	2-10	5-15	

Slow LTS-Liposomal Carrier Infusion	10-15	3-10	
Temperature Increase	12-45	5-45	10-100

[0049] Thus, as one example, the opening of the BBB can be promoted by applying the first focused ultrasound energy at a power of between about 0.001 W and about 1.00 W for a duration of less than about 1 minute to about 5 minutes. Preferably, the first focused ultrasound energy is generated using an FUS system operating at a frequency in the range of about 200 kHz to about 500 kHz. Similarly, the a temperature effective to release the therapeutic carrier from the temperature-sensitive liposomal carrier can be achieved by applying the second focused ultrasound energy at a power of about 10 W to about 100 W for a duration of about 5 minutes to about 45 minutes. Preferably, the second focused ultrasound energy is generated using an FUS system operating at a frequency that is a third harmonic of the frequency used for generating the first focused ultrasound energy (e.g., in the range of about 600 kHz to about 1500 kHz). As one example, the first focused ultrasound energy can be generated at 220 kHz and the second focused ultrasound energy can be generated at 660 kHz. In general, the time separation between the two sonications will be determined by the complete clearance of the microbubble agent from the target region, which can be assessed using the intensity of the passive maps.

[0050] Referring now to FIG. 6, a focused ultrasound ("FUS") system 600 that can be configured to implement the methods described above is shown. The FUS system 600 generally includes a transducer array 602 that is capable of delivering ultrasound to a subject 604 and receiving responsive signals therefrom. For brain applications, the transducer array 602 is preferably configured to surround an extent of the subject's head. For example, the transducer array 602 may be an approximately hemispherical

array of transducer elements.

[0051] In some embodiments, such as the one illustrated in FIG. 7, the FUS system can include two confocally aligned FUS transducers 60 in order to reduce the effective focal size in the focal region 62. As an example, the FUS transducers 60 can be oriented at between about 90 degrees and about 270 degrees relative to each other. Also, in some configurations, the FUS system can include one or more ultrasound transducers 64, or arrays of ultrasound transducers, such as a 128-element linear ultrasound array transducer (90 mm, 1 MHz central frequency) that is confocally aligned with the one or more FUS transducers 60. In this configuration, the additional ultrasound transducer 64 can be used to passively record acoustic emissions.

[0052] In some other embodiments, such as the one illustrated in FIG. 8, the FUS system can include one or more FUS transducers 70 that include an aperture 72 through which a conventional ultrasound transducer 74 can be provided. In these embodiments, the focused ultrasound transducer 70 and conventional ultrasound transducer 74 are confocally aligned with a focal region 76.

[0053] Referring again to FIG. 6, the FUS system 600 also generally includes a processor 606 that is in communication with a multi-channel transmitter 608 and a multi-channel receiver 610. The multi-channel transmitter 608 receives driving signals from the processor 606 and, in turn, directs the transducer elements of the transducer array 602 to generate ultrasound energy. The multi-channel receiver 610 receives acoustic signals during and/or after sonications and relays these signals to the processor 606 for processing in accordance with embodiments of the present invention. In some embodiments, the multi-channel transmitter 608 and a multi-channel receiver 610 can be included in a pulser/receiver that is in communication with the processor 606. In some embodiments, the multi-channel transmitter 608 and the multi-channel

receiver 610 can be included in a pulser/receiver that is in communication with the processor 606 to perform ultrasound-based thermometry.

[0054] The processor 606 may also be configured to adjust the driving signals in response to the acoustic emissions recorded by the multi-channel receiver 610. For example, the phase and/or amplitude of the driving signals may be adjusted so that ultrasound energy is more efficiently transmitted through the skull of the subject 604 and into the target volume-of-interest 612. Furthermore, the acoustic signals may also be analyzed to determine whether and how the extent of the focal region should be adjusted.

[0055] The present invention has been described in terms of one or more preferred embodiments, and it should be appreciated that many equivalents, alternatives, variations, and modifications, aside from those expressly stated, are possible and within the scope of the invention.

CLAIMS

1. A method for using a focused ultrasound system to effectuate a treatment of a tissue in a subject who has been administered a temperature-sensitive liposomal carrier containing a therapeutic agent, the steps of the method comprising:

(a) producing first focused ultrasound energy in a target region, wherein the first focused ultrasound energy is sufficient to promote passage of the temperature-sensitive liposomal carrier containing the therapeutic agent across a blood-brain barrier;

(b) producing second focused ultrasound energy in the target region after producing the first focused ultrasound energy, wherein the second focused ultrasound energy is sufficient to alter a temperature in the target region so as to trigger release of the therapeutic agent from the temperature-sensitive liposomal carrier; and

wherein release of the therapeutic agent effectuates treatment of the tissue in the target region.

2. The method as recited in claim 1, wherein the subject has also been previously administered a microbubble agent, and step (a) includes generating oscillations of the microbubble agent in the target region.

3. The method as recited in claim 2, wherein step (a) includes measuring acoustic emissions from the oscillations of the microbubble agent and adjusting the first focused ultrasound energy based on the acoustic emissions.

4. The method as recited in claim 3, wherein measuring the acoustic emissions includes passively recording the acoustic emissions.
5. The method as recited in claim 3, wherein measuring the acoustic emissions includes producing a cavitation map that depicts a type, a strength, and a location of one or more cavitation events.
6. The method as recited in claim 5, wherein the cavitation map is produced based on a backprojection of the acoustic emissions using an angular spectrum-based algorithm.
7. The method as recited in claim 3, wherein measuring the acoustic emissions includes measuring a power spectrum of the acoustic emissions.
8. The method as recited in claim 3, wherein measuring the acoustic emissions include producing a quantitative measurement of the acoustic emissions based in part on a numerical simulation that accounts for propagation characteristics of acoustic waves emitted by oscillating microbubbles.
9. The method as recited in claim 1, wherein step (b) includes measuring the temperature in the target region and adjusting the second focused ultrasound energy to increase the temperature in the target region to within an effective temperature range.
10. The method as recited in claim 9, wherein the effective temperature range is from about 38 degrees Celsius to about 45 degrees Celsius.

11. The method as recited in claim 10, wherein the effective temperature range is from about 40 degrees Celsius to about 42 degrees Celsius.

12. The method as recited in claim 9, wherein the focused ultrasound system is part of a magnetic resonance guided focused ultrasound system, and the temperature in the target region is measured in step (b) using magnetic resonance thermometry.

13. The method as recited in claim 1, wherein the tissue includes a tumor and release of the therapeutic agent effectuates treatment of the tumor.

14. A temperature-sensitive liposomal carrier containing a therapeutic agent for use according to the method as recited in claim 1.

15. The temperature-sensitive liposomal carrier as recited in claim 14, wherein the therapeutic agent comprises a chemotherapy agent.

16. The temperature-sensitive liposomal carrier as recited in claim 15, wherein the chemotherapy agent is doxorubicin.

17. The temperature-sensitive liposomal carrier as recited in claim 14, further comprising a targeting moiety having specificity to the tissue in the target region.

18. The temperature-sensitive liposomal carrier as recited in claim 17, wherein the targeting moiety comprises a monoclonal antibody.

19. The temperature-sensitive liposomal carrier as recited in claim 18, wherein the monoclonal antibody includes an anti-transferrin monoclonal antibody (OX26-mAb).

20. A focused ultrasound system for use in promoting delivery of a temperature-sensitive liposomal carrier containing a therapeutic agent to a tissue in a subject, comprising:

a transducer configured to generate focused ultrasound energy;

a controller in communication with the transducer and programmed to:

(a) control the transducer to produce first focused ultrasound energy in a target region, wherein the first focused ultrasound energy is sufficient to promote passage of the temperature-sensitive liposomal carrier containing the therapeutic agent across a blood-brain barrier; and

(b) control the transducer to produce second focused ultrasound energy in the target region, wherein the second focused ultrasound energy is sufficient to alter a temperature in the target region so as to trigger release of the therapeutic agent from the temperature-sensitive liposomal carrier.

21. The focused ultrasound system as recited in claim 20, further comprising another transducer in communication with the controller and configured to generate ultrasound energy, wherein the transducer and the another transducer are confocally aligned with the target region.

22. The focused ultrasound system as recited in claim 21, wherein the transducer is oriented to deliver focused ultrasound energy along a beam axis that is oriented at between about 90 degrees and about 270 degrees relative to a beam axis of the another transducer.

23. The focused ultrasound system as recited in claim 20, further comprising another transducer in communication with the controller and configured to passively measure acoustic emissions from the target region, wherein the transducer and the another transducer are confocally aligned with the target region.

24. The focused ultrasound system as recited in claim 23, wherein the controller is programmed to:

control the another transducer to record acoustic emissions from the target region that are generated in response to the first focused ultrasound energy; and

adjust the first focused ultrasound energy based on the recorded acoustic emissions in order to increase promotion of passage of the temperature-sensitive liposomal carrier containing the therapeutic agent across the blood-brain barrier.

25. The focused ultrasound system as recited in claim 24, wherein the controller is programmed to produce cavitation maps for different spectral components from the recorded acoustic emissions and to adjust the first focused ultrasound energy based on an intensity of the cavitation maps.

26. The focused ultrasound system as recited in claim 25, wherein the different spectral components include at least two of harmonics, ultraharmonics, subharmonics, and broadband.

27. The focused ultrasound system as recited in claim 24, wherein the controller is programmed to produce a quantitative acoustic emission measurement based in part on the recorded acoustic emissions and on a numerical simulation that accounts for a propagation of acoustic waves from a cavitation event, and wherein the controller is programmed to adjust the first focused ultrasound energy based on the quantitative acoustic emission measurement.

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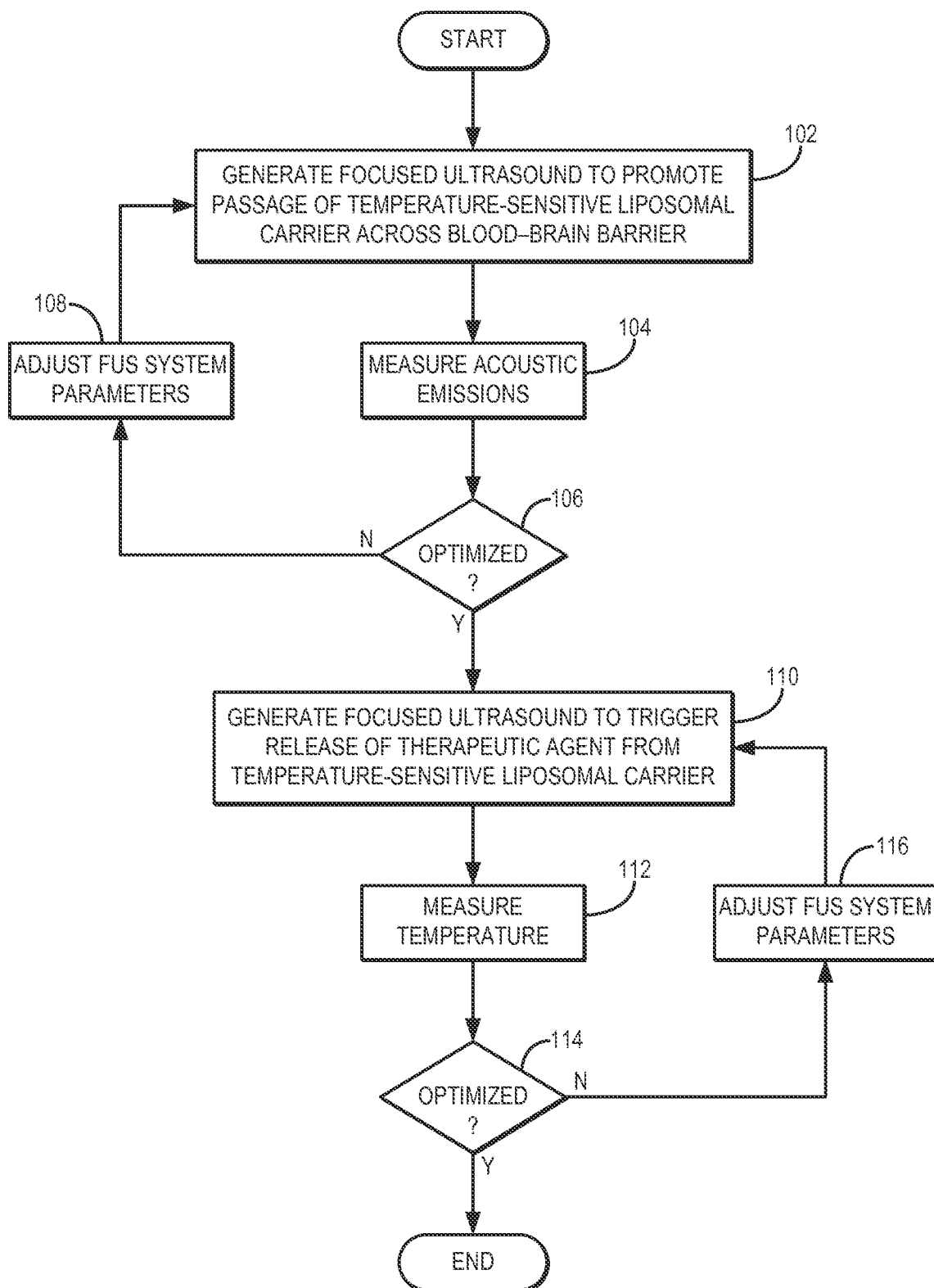


FIG. 1

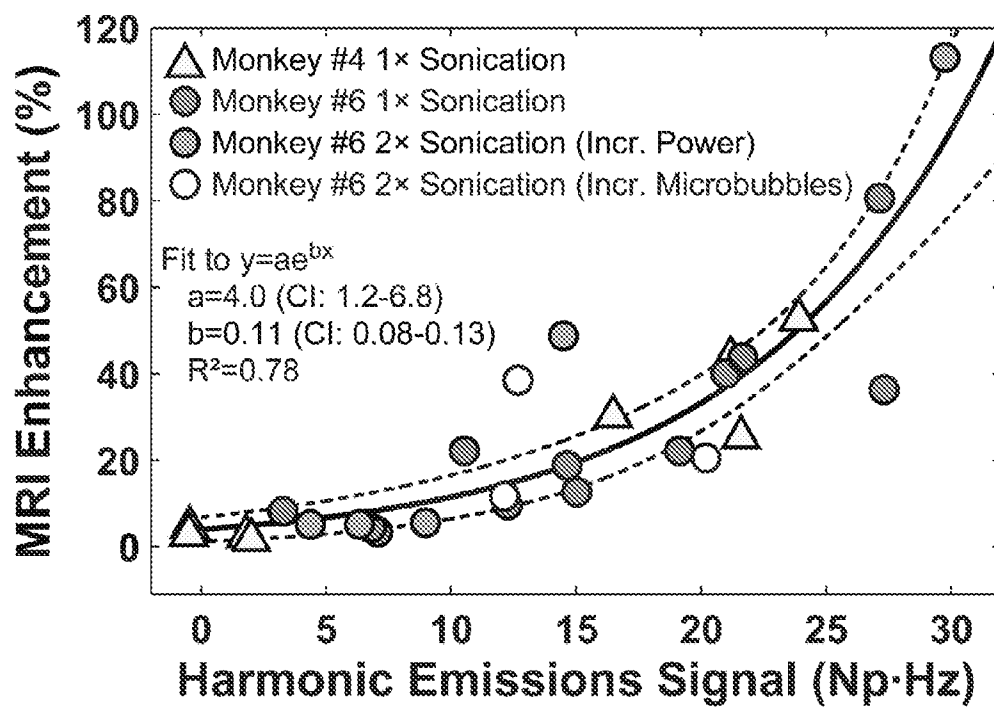


FIG. 2

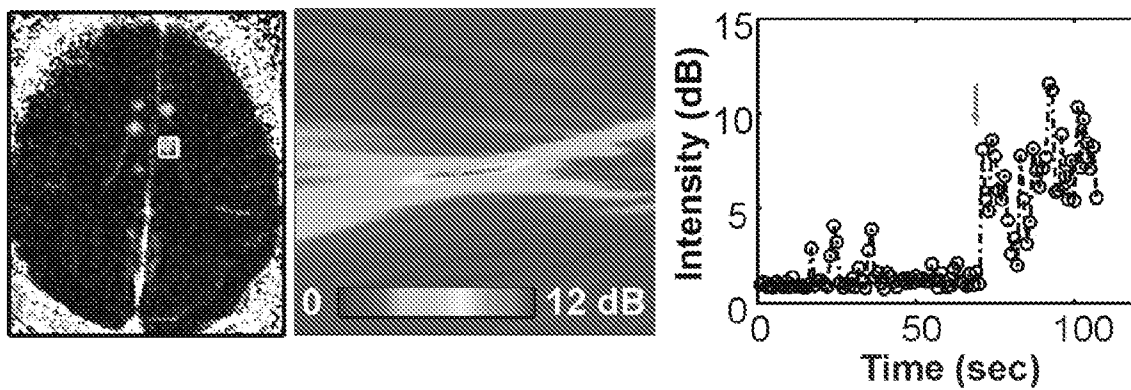


FIG. 3

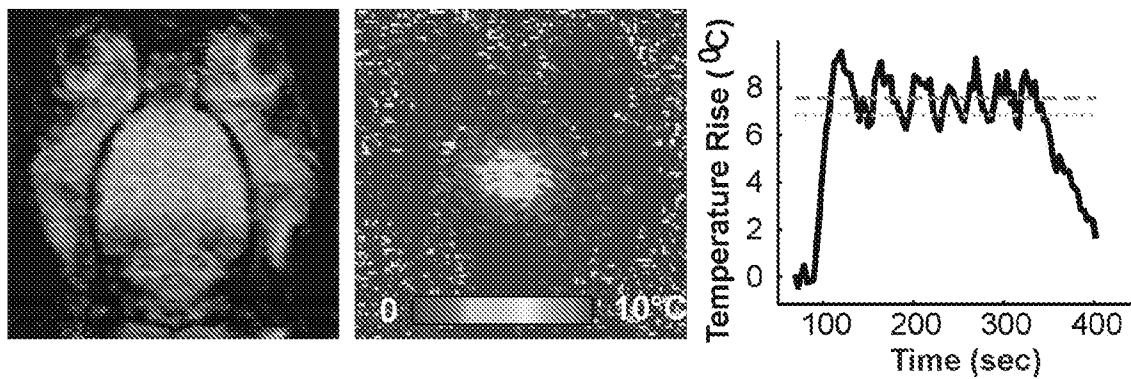


FIG. 4

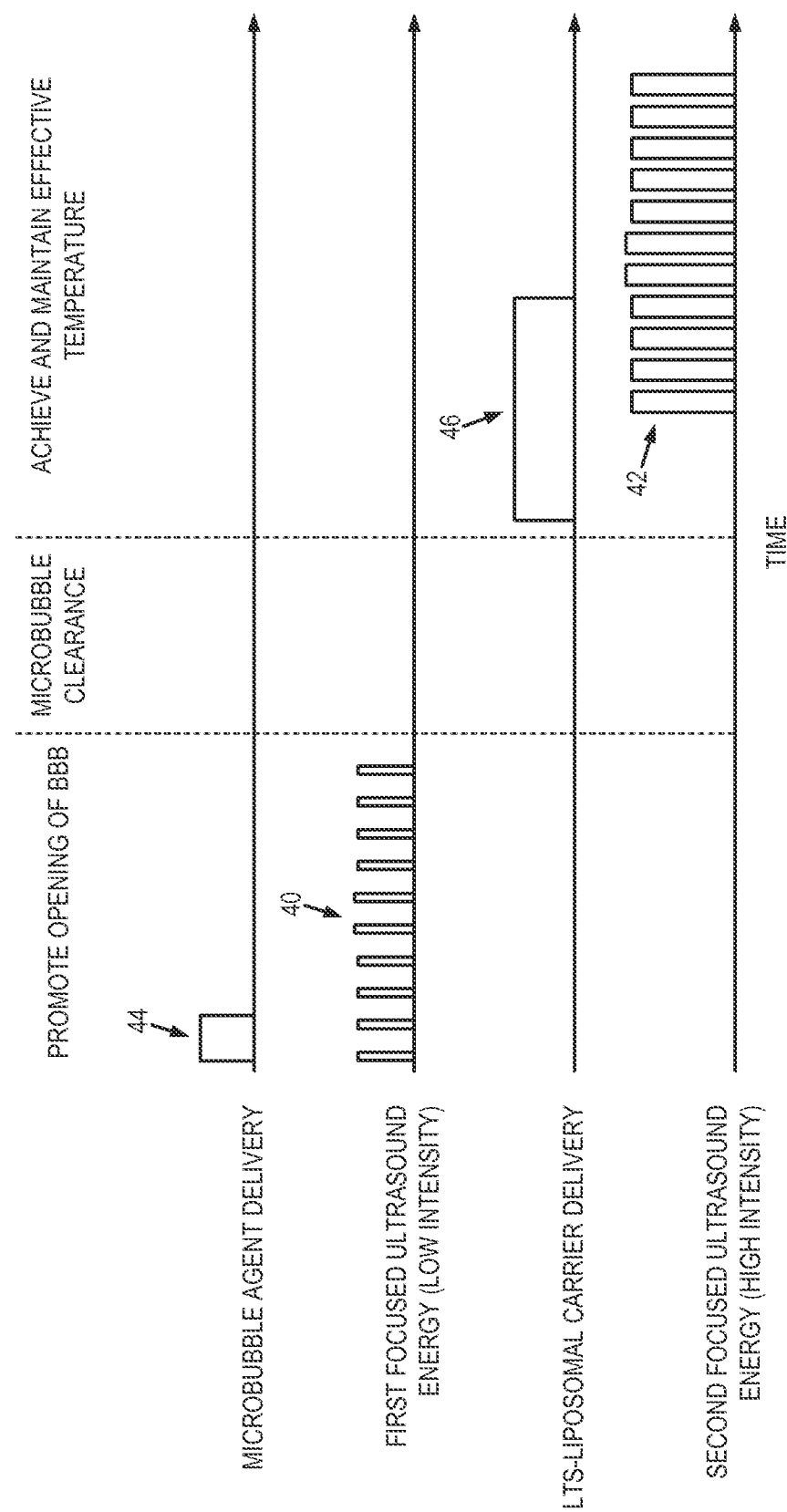


FIG. 5

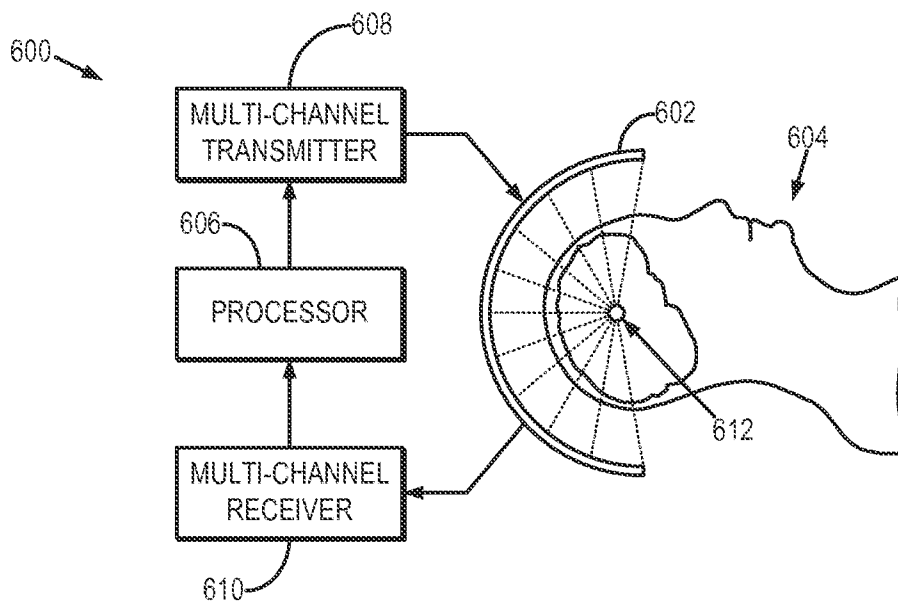


FIG. 6

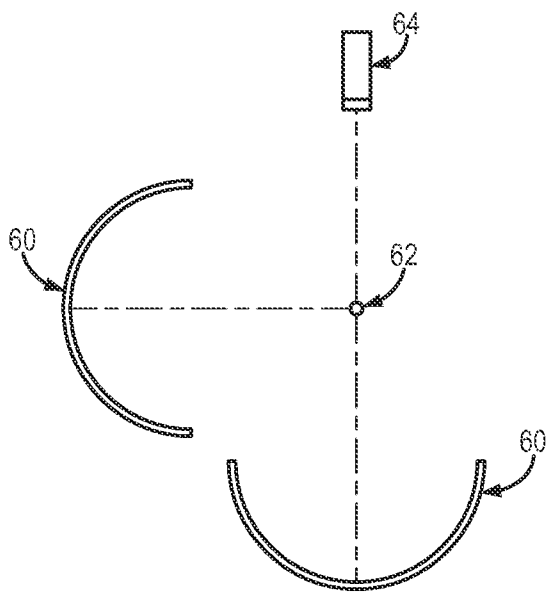


FIG. 7

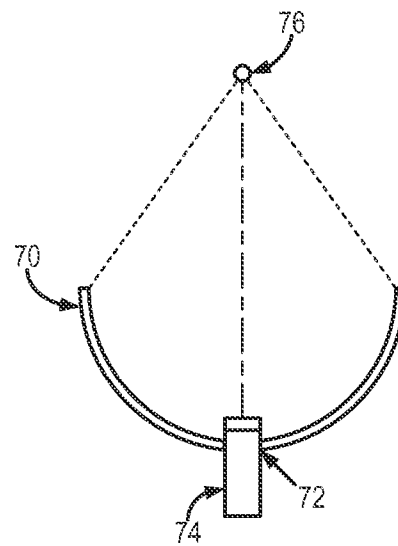


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/037590

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 47/48 (2015.01)

CPC - A61K 47/48815 (2015.09)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61B 5/05, 8/08; A61K 9/00, 9/17, 38/00, 38/40, 39/00, 47/48 (2015.01)

CPC - A61B 5/05; A61K 9/00, 9/127, 9/1271, 47/48, 47/488, 47/48815, 47/48823 (2015.09) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 424/1.69, 9.10, 9.20, 489; 600/437; 604/22

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Patents, Google Scholar

Search terms used: blood-brain barrier, ultrasound, liposomes, cavitation, bubbles, microbubbles, transferrin, chemotherapy, cross

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0141163 A1 (VITALIANO et al) 21 June 2007 (21.06.2007) entire document	1,2,13,14,17-19
Y		3-5,7,9-11,15,16,20-26
Y	US 2006/0241529 A1 (HYNENEN et al) 26 October 2006 (26.10.2006) entire document	3-5,7,20-26
Y	EP 2 305 216 A1 (KONINKLIJKE PHILIPS ELECTRONICS N.V.) 06 April 2011 (06.04.2011) entire document	9-11
Y	US 2011/0177009 A1 (LANGEREIS et al) 21 July 2011 (21.07.2011) entire document	15, 16
A	US 2012/0171118 A1 (PAPISOV) 05 July 2012 (05.07.2012) entire document	1-27
A	US 2014/0147390 A1 (EXNER et al) 29 May 2014 (29.05.2014) entire document	1-27
A	US 2013/0281916 A1 (WAGSTAFFE et al) 24 October 2013 (24.10.2013) entire document	1-27

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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

"P" document 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 cited to understand the principle or theory underlying the invention

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 September 2015

Date of mailing of the international search report

29 SEP 2015

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