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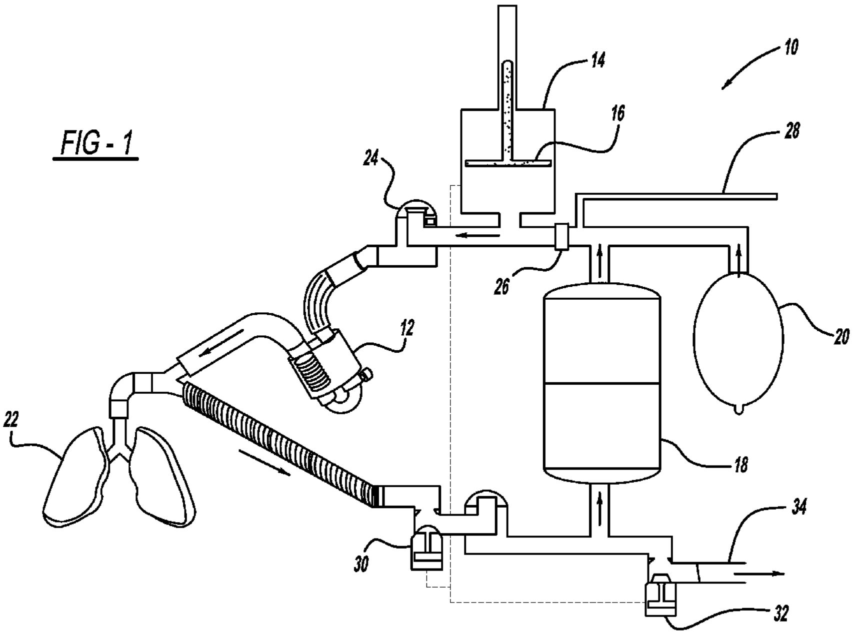

FIG - 1

(57) Abstract: A breathing system for hyperthermic assisted radiation therapy includes at least one heating element that modulates the temperature of air inhaled by a patient, at least one cooling element that modulates the humidity of the air inhaled by a patient, and a controller that maintains the desired humidity and temperature.

HYPERTHERMIA ASSISTED RADIATION THERAPY

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/216,587, filed May 19, 2009, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] The present invention relates generally to radiation therapy. More particularly, the present invention relates to hyperthermia assisted radiation therapy.

[0003] Lung cancer is the most common fatal cancer in the United States for men aged 40 years and older and women aged 60 years and older. Inoperable lung tumors are primarily treated using radiation therapy. Recent studies in radiation therapy of lung tumors have shown that higher radiation dose delivered to the target has been associated with improved tumor control. However, a major therapeutic concern is represented by tumor hypoxia where hypoxic cells require three times more dose than a well oxygenated cell to achieve the same level of cell deaths. When cells gradually become hypoxic they adapt by up-regulating the production of numerous proteins that promote their self-survival. These proteins slow the rate of growth, stimulate growth of new vasculature, inhibit apoptosis, and promote metastatic spread. The direct consequence of these changes is that patients with hypoxic tumors invariably experience poor outcome to treatment, hypoxia also being the primary inhibitor of chemotherapy effectiveness.

BRIEF SUMMARY

[0004] In view of the drawbacks and limitations of the known technologies, a breathing system for hyperthermic assisted radiation therapy (HART) includes at least one heating element that modulates the temperature of air inhaled by a patient, at least one cooling element that modulates the humidity of the air inhaled by a patient, and a controller that maintains the desired humidity and temperature in accordance with the invention.

[0005] Some embodiments may include one or more of the following advantanges:

[0006] The HART technique generates a better local tumor control with significant, synergistic enhancement of clinical outcome. The method can reduce the number of treatment fractions due to the enhanced local tumor control. The breathing system can be integrated with a linear accelerator. As such, along with image guidance, the online data provided by the system allows the medical personnel to explore several gating strategies based on the separate or combinations of breathing parameters. This in turn can add to the synergistic effect of HART. The HART technique can improve patient well being during the treatment. The system and method will not interrupt the current treatment flow, requires no additional dose to the patient and presents only minimal risk. Modern breathing systems precisely synchronize ventilation to the patient's breathing requirements, helping to minimize the work of breathing and therefore assisting the patients in achieving a calm, regular breathing state.

[0007] The system can be a portable, robust technology to safely induce hyperthermia at the lungs tissue level as an adjuvant treatment to be delivered simultaneously with radiotherapy. The developed technology can be the basis for enhancing the clinical outcome by combining HART with adjuvant therapies relying on compatible radiosensitizers for lung tumors.

[0008] The foregoing discussion has been provided only by way of introduction. Additional features, benefits and advantages of the present invention will become apparent from the subsequent description and the appended claims, taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The accompanying drawings, incorporated in and forming a part of the specification, illustrate several aspects of the present invention and, together with the description, serve to explain the principles of the invention. The components in the figures are not necessarily to scale. Moreover, in the figures, like reference numerals designate corresponding parts throughout the views. In the drawings:

[0010] FIG. 1 shows a breathing system design including a temperature and humidity controller in accordance with the invention;

[0011] FIG. 2 shows a portable continuous positive airway pressure (CPAP) ventilator with O_2 mixers;

[0012] FIG. 3 shows a monitor screen for the system of FIG. 1 employed to monitor and record respiratory parameters;

[0013] FIG. 4 is a detail view of the temperature and humidity controller of FIG. 1 used to control temperature and humidity of the inhale air in accordance with an embodiment of the present invention;

[0014] FIG. 5 shows the effect of relative humidity on the temperature of the exhaled air;

[0015] FIG. 6 shows radiosensitization after simultaneous 2 Gy X-irradiation and 10 minute heat treatment;

[0016] FIG. 7 shows an intrabronchial (i.b.) implantation technique; and

[0017] FIG. 8 shows haematoxylin and eosin stained lung sections showing representative changes in alveolar structure with time after irradiation.

DETAILED DESCRIPTION

[0018] Major benefits may be achieved by the addition of heat to radiation therapy and chemotherapy. Heat-induced biological effects act as strong adjuvant for the radiation therapy and are effectively used in cancer treatment to kill cancer cells at different stages of growth. Heat-mediated tumor reoxygenation is attributed to increased vascularization and increase in oxygen local pressure (pO_2). Also, the damage repair mechanisms are inhibited where induction of chromosomal aberrations increased with heat-induced radiosensitization. Hyperthermia may be able to modulate the immune system by inducing the expression of heat-shock proteins (HSP). HSP isolated from cancer cells are able to induce a cytotoxic T-cell-activation against the tumor. Moreover, there is a temperature-dependant inhibition of DNA-repair enzymes, DNA-polymerases-α and $-\beta$. Accordingly, because of the anatomy and physical properties of the lung, there is a need to elevate and control the lung tissue temperature at levels needed to induce the radiosensitizing response.

[0019] Referring now to FIG. 1, a breathing system embodying the principles of the present invention is illustrated therein and designated at 10. As its primary components, the system 10 includes a temperature and humidity controller 12, a ventilator 14 with a ventilator piston 16, an absorbent canister 18, and a reservoir 20. An intake valve 24 and a decoupling valve 26 control the flow of air through the temperature and humidity controller 12 to the patient's lungs 22, typically through a mask 52 (FIG. 4), while a pair of exhaust or exhalation valves 30, 32 in coordination with the ventilator 14, control the exhaust exhaled from the patient's lungs 22.

[0020] Fresh air is supplied through an inflow line 28 and flows directly to the lungs 22 and also fills the reservoir 20 which supplies further fresh air when needed. The exhaust from the lungs 22 are expelled from the system 10 through an exhaust line 34 when the exhaust valves 30 and 32 are open. The exhaled air may also be directed to the absorbent canister 18 when the valve 32 is closed.

[0021] To further improve the clinical outcome in the case of lung tumors, the air the patient breathes is a thermal delivery vector to induce hyperthermia at the lung tissue level. Moreover, the vector can be used to efficiently deliver specific radiosensitizers mixed in the breathing air. Therefore a robust breathing system controls the temperature of the lung tissue within the hyperthermic regime (about 41-43°C) in accordance with the invention.

[0022] Local tumor control is accomplished by exposing the lung tumors to a synergetic cancer treatment system that encompasses the use of hyperthermia and specific radiosensitizing factors in addition to the conventional dosimetric escalation and cytotoxic drugs. Hyperthermia assisted radiation therapy (HART) provides enhanced local tumor control for lung cancer disease.

[0023] Because of the heat-mediated tumor reoxygenation, radiosensitizers are gas mixtures that contain elevated concentrations of oxygen (hyperoxic gas). Damage to DNA is primarily induced by interaction with oxygen radicals (for example, hydroxyl radical, superoxide anion) formed by the ionization of water surrounding the DNA. The damaged ends of DNA can react with the nearby oxygen to form stable, organic peroxides that are difficult repair, increasing the mitotic death propensity. A higher oxygen concentration in the inhaled air results in increased blood oxygen concentration. Alternatively, a combination of hyperoxic gases and vasodilating drugs can be also used. Reversely, in the case of radiotherapy treatments for tumors located in the upper abdomen (liver, pancreas), where the lungs are organs at risk for radio-contamination, the breathing device (in the no-heat regime) can be used to deliver lung-specific radioprotectants.

[0024] The breathing system 10 is capable of safely raising and controlling the temperature of the lung tissue with minimal disruption of the present treatment flow. The temperature of the lung tissue is measured and calibrated non-invasively using magnetic resonance temperature imaging (MRI thermometry). The system 10 provides targeted radiosensitizers for lung tumors that can be safely aerosolized and mixed in the breathing air.

[0025] The ventilator 14 has continuous positive airway pressure (CPAP) control which is regulated by a restriction of flow to the exhalation valve 30. CPAP provides continuous positive airway pressure in the breathing circuit as the patient breathes spontaneously. This keeps the alveoli and airways inflated by preventing proximal airway pressure from returning to zero at the end of exhalation. CPAP is applied to patients who can breathe spontaneously and do not require full ventilatory support. It can improve lung volume and, consequently, oxygenation and lung function by increasing alveolar volumes, recruitment, and stability. By helping to redistribute interstitial water, CPAP also improves O_2 diffusion across the alveolar capillary membrane.

[0026] Referring to FIG. 2, there is shown a CRAP ventilator 14 that provides a computer interface for data acquisition. Such systems can provide the general thermodynamic breathing parameters (exhale/inhale volume, pressure, O_2 concentration) during the radiotherapy treatment. They also deliver gas mixtures at controllable concentrations. An infrared transducer and a visible spectrum transducer can be integrated in the breathing mask to measure the CO_2 and O_2 concentrations. The parameters are recorded by a central acquisition system, such as, for example, the NI (National Instruments Corporation, Austin,TX) platform that includes the data acquisition hardware (DAQ) and the controlling software, which provides a user interface to monitor and record the respiratory parameters as shown, for example, in FIG. 3.

[0027] Referring FIG. 4, further details of the temperature and humidity controller 12 are illustrated. The temperature and humidity controller 12 receives air from the ventilator as indicated by the arrow 50 and supplies air at the desired temperature and humidity to a mask 52 worn by the patient who inhales the treated air. The temperature and humidity controller 12 further includes a heating element controller 54 and a Peltier element controller 56 to adjust or modulate the temperature and humidity, respectively, of the inflowing air. The humidity of the air is monitored by a humidity sensor 58 which receives signals from a water condenser 60. The signal from water condenser 60 indicates the amount of water in the fresh air flowing from the ventilator. The temperature and humidity controller 12 also includes an inhalation temperature sensor 62 and an exhalation temperature sensor 64 that monitors the inlet and exhaust temperature to and from the patient, respectively. The information from the sensors 62 and 64 are fed to the heating element controller 54 which in conjunction with a fan controller adjusts the fresh air to the desired temperature. The temperature sensors 62, 64, the humidity sensor 58, the Peltier element controller 56, the heating element controller 54, and the fan controller 66 provide information to a feedback system or loop 70 under the direction of a CPU such as, for example, a computer 72. The sensors 62 and 64 may be located in the mask 52. The humidity sensor 58, the Peltier element controller 56, the heating element controller 54, and the fan controller 66 may be contained in a housing 13 which also contains the heating elements 15, a fan 17, and Peltier cooling elements 19.

[0028] The temperature and humidity control system 12 allows the patient to freely breathe air at temperatures between about $45^{O}C$ to $55^{O}C$ (with minimal effort). This will induce a thermal steady state (TSS) in the lung tissue with temperatures in the range of about $41^{O}C$ to $43^{O}C$. The feedback loop 70 modulates the relationship between the inhaled air temperature and the exhaled air temperature to achieve a thermal steady state inside the lungs. The lung thermal steady state is defined as the state where the exhale air temperature is within the range of about 41^{O}C to 43 ^{O}C hyperthermic regime. Once a relative steady state is attained, the radiotherapy treatment is ready to be initiated.

[0029] The lung tissue temperature varies as a function of the respiratory inhalation or exhalation phase. Because of the lung physiology, the range of temperature fluctuations can also be influenced by controlling the relative humidity (RH) inhaled air. The higher the humidity the smaller is the difference between inhaled and exhaled air temperatures as indicated in FIG. 5. In particular, FIG. 5 shows the relative humidity effect on temperature of the exhaled air. It is desirable to achieve a relative steady state with temperature variations confined within the hyperthermic regime (of about 41^{O}C to 43^{O}C). However, the relative humidity effect is analyzed and controlled since humid air (RH>70%) is more difficult to breathe and lung cancer patients often have reduced respiratory function. Accordingly, an optimal combination between air temperature and relative humidity is desired to comfort patients' needs. Nevertheless, RH typically does not exceed about 65%. Preferably, the RH is about 60%.

[0030] Humidity control with the Peltier element controller 56 is achieved with the series of cascaded Peltier cooling elements 19 (thermoelectric effect), which cool down the incoming gas to facilitate water condensation that collects in the water condenser 60. The air humidity is measured by the humidity sensor 58 and constantly read by the feedback system or loop 70. In turn, the feedback loop 70 controls the current that feeds the cooling system to achieve the appropriate humidity level. For the cooling system to work efficiently, the 'hot' side is appropriately vented. This is accomplished by using the cooling fan 17, under the direction of the fan controller 66, which directs the heat generated by the Peltier elements 19 towards the air heating region of the system. Since air cooling efficiency depends on how fast heat is transported away, the fan speed is also controlled by the feedback loop 70. Based on the temperature of the exhaled air, as detected by the exhalation temperature sensor 64, the feedback loop 70 controls the air heating elements 15. The feedback controller within, for example, the computer 72, features proportional, integral, and derivative (PID) control that provides exceptionally tight control of air temperature and humidity. The feedback algorithm contains an auto-tuning feature that helps to ensure maximum performance over a broad spectrum of operating conditions (for example, fast/slow rate breathing and shallow/deep breathing). Auto-tuning sets the critical PID terms to match the conditions of the application and provides fast response while minimizing overshoot and undershoot. A couple of sensor alarms that monitor the upper temperature and humidity limits are located at the inhalation terminal and at the air heating controller. Their roles are redundant with the feedback loop sensors and provide an emergency switch-off function if temperature and/or humidity exceed the preset upper limit.

[0031] In another arrangement, the humidity sensor is located in the mask 52. Signals are sent from the humidity sensor in the mask directly to the heating element controller 54. In turn, information from the heating element controller 54 is sent to the Peltier element controller 56 which adjusts the amount of vaporization occurring in the housing 13, where the water condenser 60 may act as a reservoir for humidification of the air.

[0032] As shown in FIG. 5, the exhaled air temperature, can easily reach temperatures needed to induce a hyperthermic regime at the lung tissue level. However, the temperature of the lung tissue may depend on how deep the patient breathes. To address this, a series of non-invasive, MRI thermometry analyses under different respiratory conditions (temperature, humidity, oxygen concentration and breathing depth) is performed. The approach to clinical MR thermometry uses the change in resonance frequency of water protons with temperature or selective detection of intermolecular multiple quantum coherences. The data obtained is employed to calibrate the temperature control feedback loop 70 in order to obtain the optimal set of parameters necessary to induce the hyperthermic response.

[0033] The following examples illustrated features and principles of the present invention but are not meant to limit the scope of the present invention.

[0034] EXAMPLE 1: In Vitro investigation of HART applied to lung adenocarcinoma cells

[0035] Modest sensitization of A549 lung adenocarcinoma cells was evident after a 10 min treatment of 45°C (surviving fraction (SF) = 0.81±0.03). This was markedly increased by 30 minute (SF=0.12±0.01) and 60 minute treatments

(SF=0.002±0.0001). Radiosensitization was demonstrated after 2 Gy X-irradiation with simultaneous heat exposures. Survival was reduced from 0.81±0.03 (heat only) to 0.34±0.03 (heat+radiation) for a 10 minute thermal treatment (FIG. 6) and from 0.12±0.01 (heat only) to 0.01±0.002 (heat+radiation) for 30 minute thermal treatment. By comparison, a single x-ray dose reduced survival to 0.64±0.03.

[0036] These thermal-radiosensitizing effects may translate into a complex 3D tissue model to establish and define the role of blood flow in regulating temperature in solid pulmonary tumors and surrounding normal lung tissue. A murine model was used for pragmatic reasons of cost and to utilize the small animal imaging device (described below). Simultaneous radiation and heat is given to ensure thermal radiosensitization, rather than additional thermal cytotoxicity that is obtained when hyperthermia is given pre or post irradiation.

[0037] EXAMPLE 2: In vivo investigation of HART applied to small animals

[0038] A model using orthotopic implanted human pulmonary tumors can be employed. The A549 adenocarcinoma cells were chosen for a previous in vivo tumor growth delay studies because these tumors are relatively resistant to many cancer therapies and are highly metastatic to the lungs from subcutaneous implants. However, tumors can be established directly in the lungs of female nude mice. As shown in FIG. 7, an implantation technique for the growth of human lung cancer cell lines in the bronchioloalveolar region of the right lung via intrabronchial (i.b.) injection with a syringe 100 into the bronchial tubes 102 is employed. The shaded area 104 in FIG. 7 represents the caudal lobe of the right lung, the area where the majority of tumor cells are localized following i.b. implantation. Tumor-bearing animals implanted with this technique become progresssively cachexie and dyspneic following implantation. Tumors grow predominately in the pleural space and subsequently invaded the lung parenchymal and/or chest wall structures. An overall tumor-related mortality of 92% is observed within 50 days after a 1 x 10^6 A549 tumor cell inoculum. Local mediastinal invasion is observed. Animals bearing the lung carcinomas can be treated with localized pulmonary X-irradiation targeted to the tumor site using a 160 KVp Faxitron X-ray cabinet (model 43855F, Wheeling, Illinois). Three fractions of 5 Gy is given over five days to mimic clinical hypofractionation schedules. Radiation treatment occurs on days 7-11 post-tumor cell implantation when the tumors are about 100 mm^3 in volume. Tumor volume will be determined by SPECT/CT imaging using a GammaMedica FLEX Triumph™ system small animal imager. Blood flow is considered with respect to the extent of tumor hypoxia as determined by PET scans using ^{F18}FDG. Throughput for PET/CT is 5-15 animals depending on the protocol, and SPECT/CT is 2-20 animals depending on the protocol. Imaging is used to target the pulmonary irradiations. The primary endpoint is tumor volume. Treatment efficacy for RT alone, 10 minutes air-breathing at 45°C alone and simultaneous RT combined with 10 minutes air-breathing at 45°C is statistically compared. A final group of animals is sham treated for determine untreated tumor growth rate. RT only animals is exposed to the same breathing regimen and the hyperthermia animals excluding the heating, while heat only animals is sham-irradiated. To allow for variation in tumor growth rates and tumor take rates between animals 20 animals per treatment group are employed.

[0039] The lungs are isolated from all treated animals and examined for therapy-related changes to histology compared with sham-treated controls. FIG. 8 illustrates the change in lung architecture for haematoxylin and eosin stained lung sections that is seen 48 hours and 4 weeks post irradiation with a single dose of 2 Gy X-rays in the absence of heat. The lung sections show representative changes in alveolor structure with time after irradiation. The largest increases in alveolar septa can be seen at the early times after radiation exposure. These include thickening of the alveolar septa and invasion of inflammatory cells.

[0040] An automated mathematical scoring algorithm was developed based on segmentation analysis to determine the extent of pulmonary injury that is used to classify injury in this study. This is employed in combination with physical measurements of alveolar septal thickness obtained from H&E high magnification microscopy (40x objective) and a manual assessment of changes in tissue architecture using a manual 4-point scale made at low magnification (10x objective), which considers the invasion of inflammatory cells such as neutrophils, macrophages and lympohocytes. Immunohistochemistry staining for cytokines and chemokines is performed to determine the underlying molecular mechanisms regulating these changes in tissue structure. Tumor specific markers and cell proliferation (ki67, cyclin D) and hypoxia biomarkers (GLUT1, CA9) is conducted and these data compared with tumor measurements from the SPECT/CT scanning. Blood serum samples are analyzed for treatment-induced changes in circulating cytokines using a Multiplex Bead Array Assay system for detection of soluble circulating cytokines (Luminex systems). This provides a comparison of response of tumor and normal tissues to the heat and radiation treatments.

[0041] EXAMPLE 3: Clinical implementation

[0042] The system 10 described is employed on the investigations on small animals where the air volume circulated is relatively small and easy to control. For the clinical translation application, where human subject is involved, a heated breathing tube is employed to minimize air heat loss due the larger air volumes, and it is incorporated in the ventilator 14 and temperature control feedback loop 70.

[0043] Respiratory parameters (volume, flow, inhalation/exhalatino pressure, CO_2, O_2 concentrations, temperature) are measured by the machine's mouthpiece 52 and results are displayed on the control room monitor, as displayed, for example, in FIG. 3. This provides a combination of parameters that can be used for gating a linear accelerator that provides a radiation source for radiotherapy.

[0044] If gating is employed (~ 5% of lung cancer cases) the clinician and the patient work together to establish the appropriate parameter to gate based on the patient's condition. This information is saved in a breathing coordinator system (such as the Active Breathing Coordinator™ system) as a patient-specific file. A comfortable patient is less likely to move during irradiation. Since the temperature controlled ventilator (TCV) 14 is designed to be fully portable, patients can practice with the device before treatment without tying up a treatment room unnecessarily. The patient can override the heating system using a thumb switch. The abort option gives the patient confidence and a sense of active participation in the treatment. Though the HART technique does not add significant additional time on to the treatment, routine clinical usage a user-friendly method in routine clinical usage is employed to quickly implement it.

[0045] The following references are incorporated herein by reference in their entirety:

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[0046] The foregoing as well as other embodiments are within the following claims.

CLAIMS

1. A breathing system for hyperthermic assisted radiation therapy comprising:

at least one heating element that modulates the temperature of air inhaled by a patient;

at least one Peltier element that modulates the humidity of the air inhaled by a patient; and

at least one controller that maintains the desired humidity and temperature of the air inhaled by the patient.

2. The breathing system of claim 1 wherein the at least one heating element modulates the temperature of the air such that the temperature of the air inhaled by the patient is between about 45^{O}C to 55^{O}C.

3. The breathing system of claim 1 wherein the system induces a thermal steady state in the patient’s lung tissue with temperatures in the range of about 41^{O}C to 43^{O}C.

4. The breathing system of claim 1 wherein the at least one Peltier element modulates the a humidity of the air such that the relative humidity of the air is less than about 65%.

5. The breathing system of claim 2 wherein the at least one Peltier element modulates the a humidity of the air such that the relative humidity of the air is less than about 60%.

6. The breathing system of claim 1 further comprising a humidity sensor that determines the relative humidity of the air being received by the system.

7. The breathing system of claim 1 further comprising a fan that blows air at a desired air speed over the at least one heating element.

8. The breathing system of claim 7 further comprising a fan controller adjusts the desired air speed.

9. The breathing system of claim 1 wherein the at least one controller includes a heating element controller that adjusts the at least one heating element to heat the air to a desired temperature.

10. The breathing system of claim 1 wherein the at least one controller includes a Peltier element controller that adjusts the at least one Peltier such that the air is at a desired humidity.

11. The breathing system of claim 1 further comprising a first temperature sensor that measures the temperature of the air inhaled by the patient.

12. The breathing system of claim 11 further comprising a second temperature sensor that measures the temperature of the air exhaled by the patient.

13. The breathing system of claim 1 further comprising a CPU, the at least one heating element, the at least one Peltier element, and the at least one controller forming a feedback loop that is under the direction of the CPU.

14. The breathing system of claim 13 wherein the feedback loop modulates the relationship between the air temperature inhaled by the patient the temperature of the gases exhaled by the patient to achieve a thermal steady state inside the patient’s lungs.

15. The breathing system of claim 13 wherein the feedback loop includes proportional, integral, and derivative control.

16. A method for hyperthermic assisted radiation therapy comprising:

modulating the temperature of air inhaled by a patient with at least one heating element;

modulating the humidity of the air inhaled by a patient with at least one Peltier element; and

maintaining the desired humidity and temperature of the air inhaled by the patient with at least one controller.

17. The method of claim 16 wherein the modulated air temperature inhaled by the patient is between about 45°C to 55°C.

18. The method of claim 16 wherein modulating the air temperature induces a thermal steady state in the patient's lung tissue with temperatures in the range of about 41°C to 43°C.

19. The method of claim 16 wherein the modulated humidity of the air inhaled by the patient is less than about 65%.

20. The method of claim 19 wherein the modulated humidity of the air inhaled by the patient is less than about 60%.

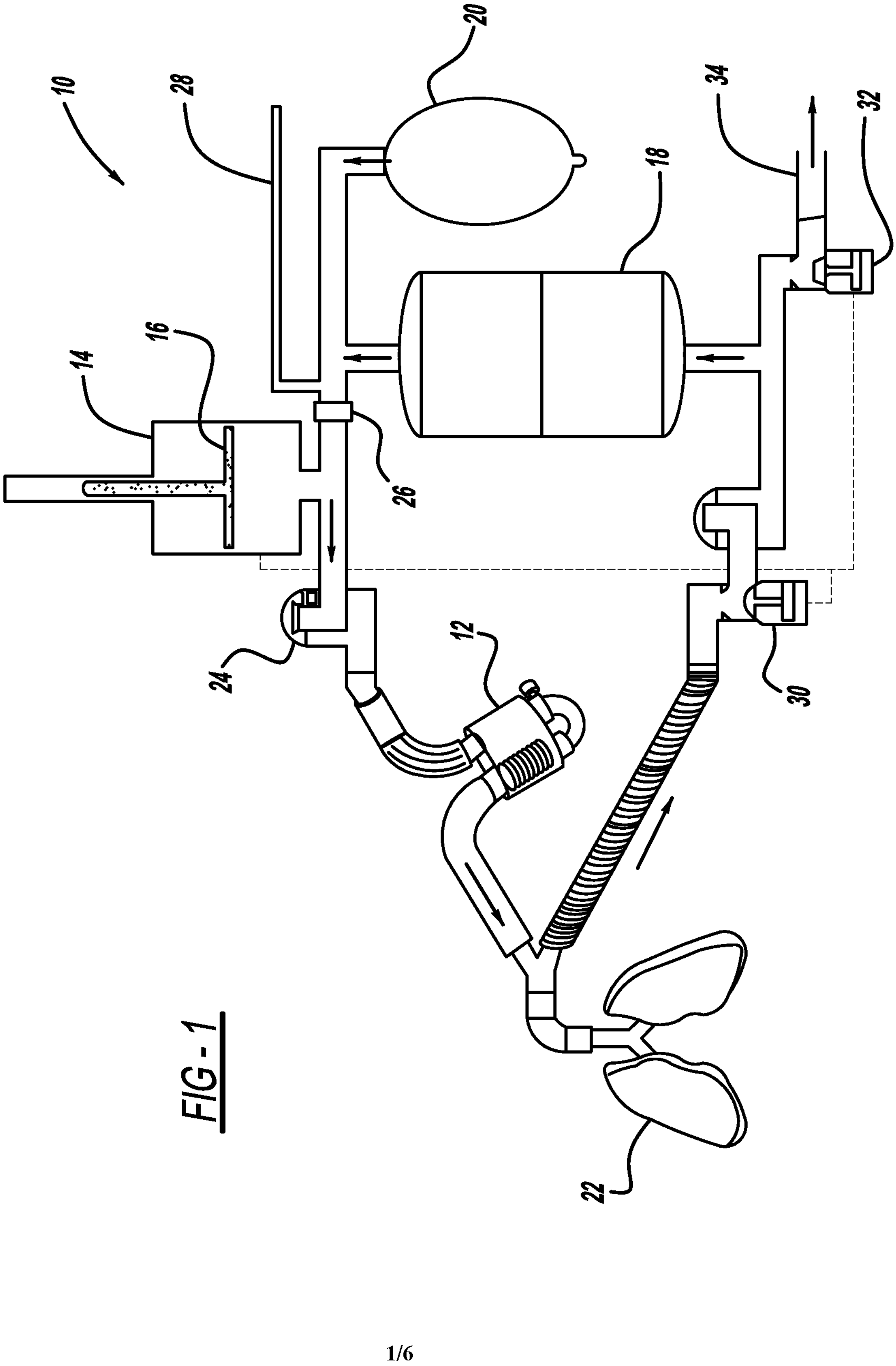


FIG - 1

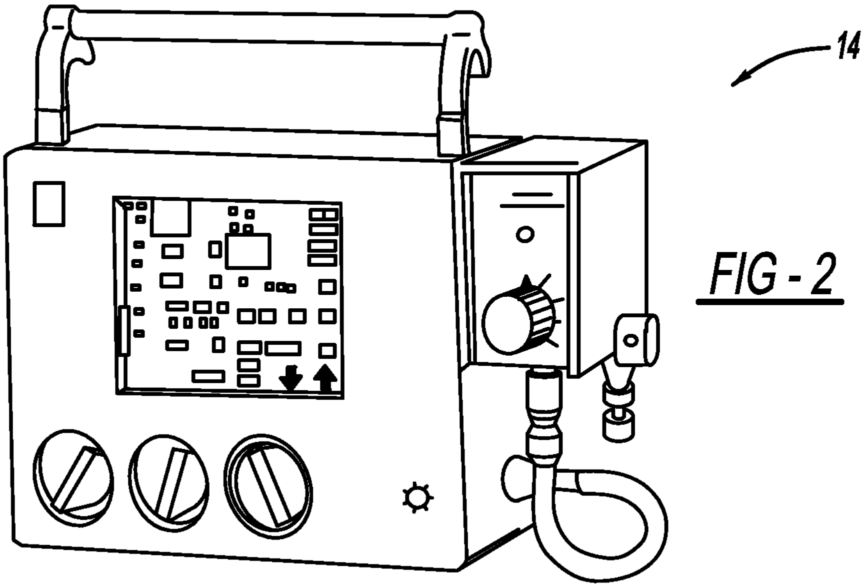
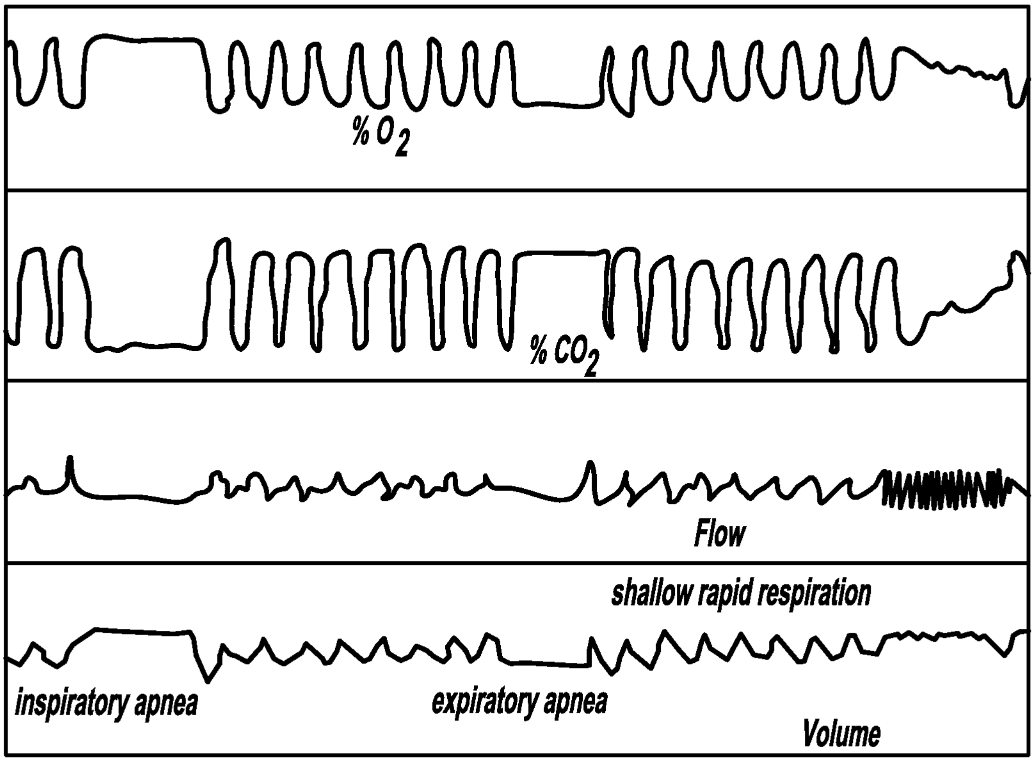

14

FIG - 2



$\%O_2$
$\%CO_2$
Flow
shallow rapid respiration
inspiratory apnea
expiratory apnea
Volume

FIG - 3

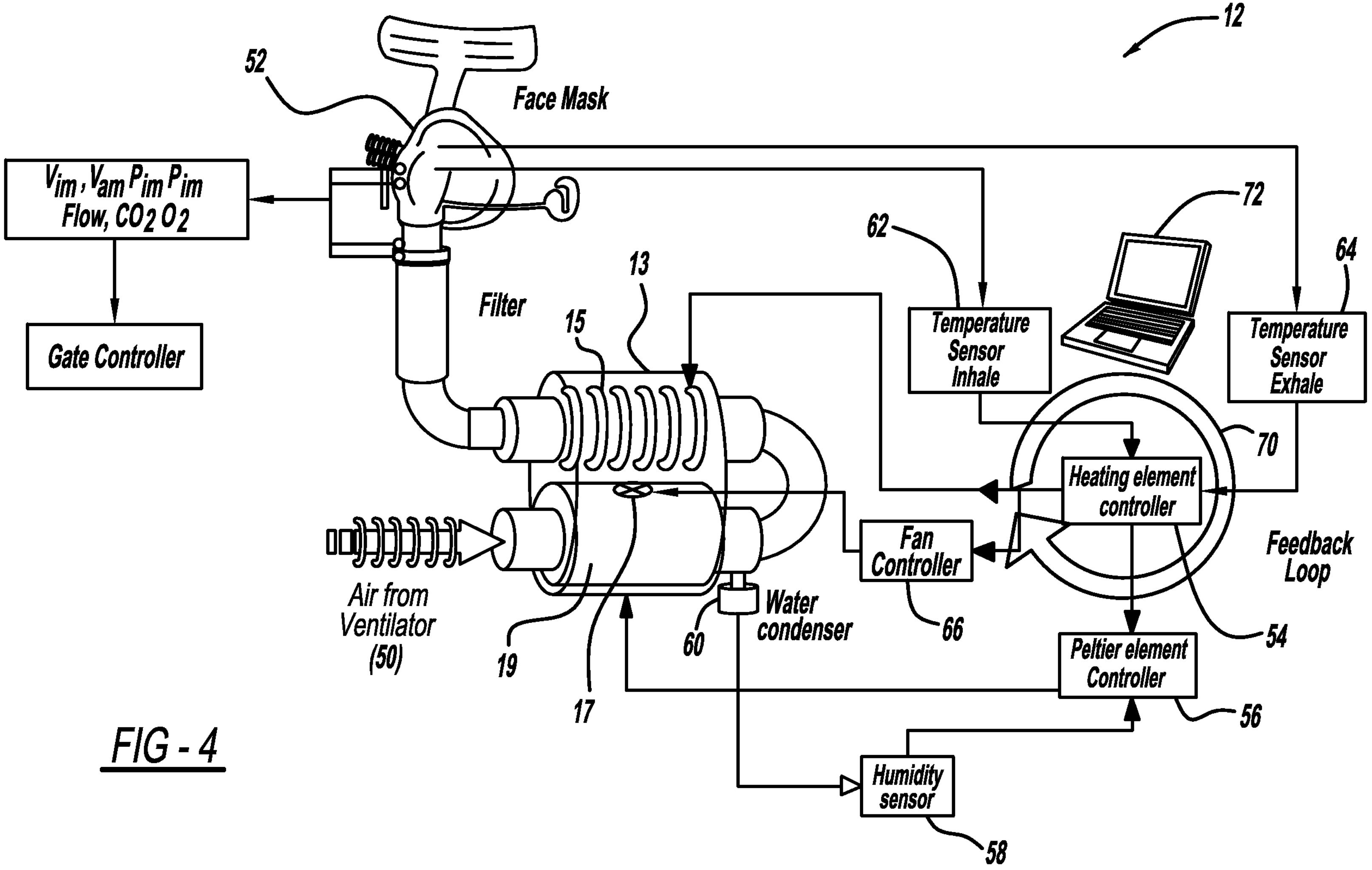

12
52
Face Mask
$V_{im}, V_{am} P_{im} P_{im}$
Flow, CO_2 O_2
Gate Controller
Filter
72
62
64
Temperature Sensor Inhale
Temperature Sensor Exhale
13
15
70
Heating element controller
Feedback Loop
Fan Controller
Air from Ventilator (50)
19
17
60
Water condenser
66
54
Peltier element Controller
56
Humidity sensor
58

FIG - 4

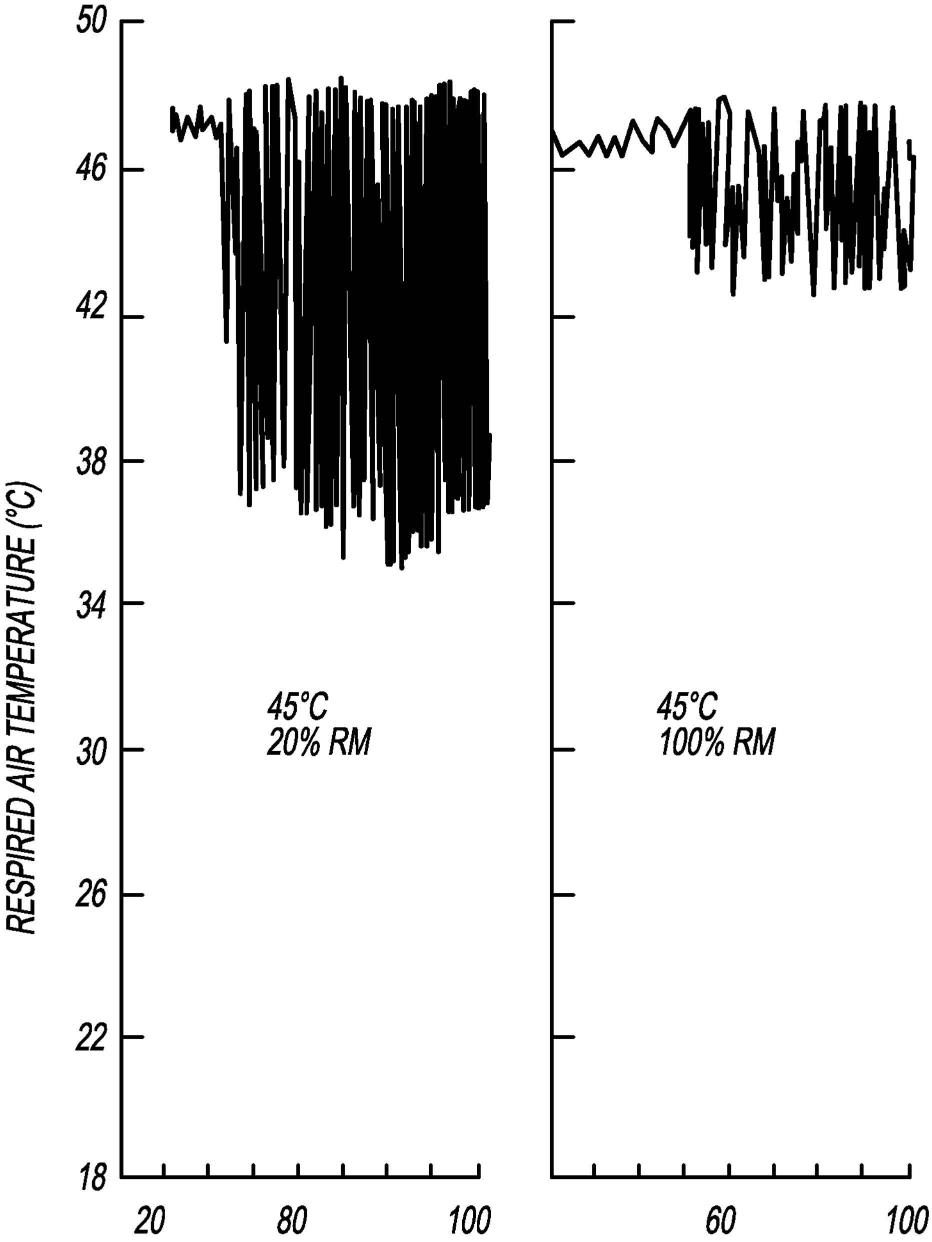

RESPIRED AIR TEMPERATURE (°C)
50
46
42
38
34
30
26
22
18
20
80
100
60
100
45°C
20% RM
45°C
100% RM

FIG - 5

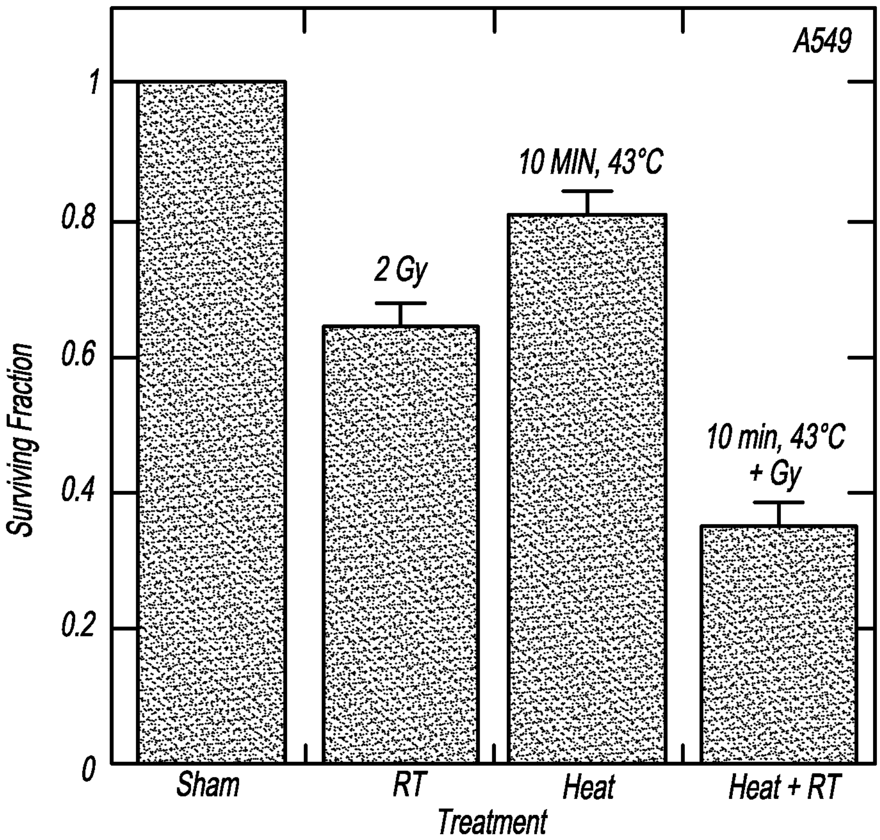

A549
Surviving Fraction
0
0.2
0.4
0.6
0.8
1
2 Gy
10 MIN, 43°C
10 min, 43°C
+ Gy
Sham
RT
Heat
Heat + RT
Treatment

FIG - 6

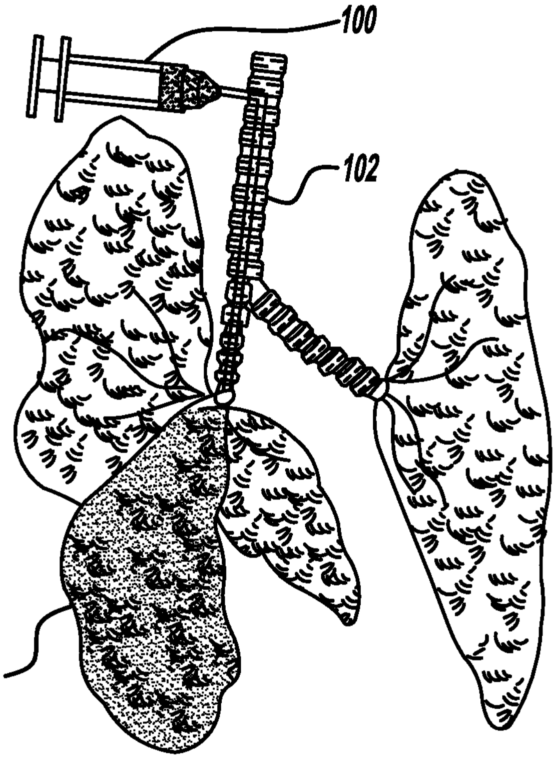

100
102
104

FIG - 7

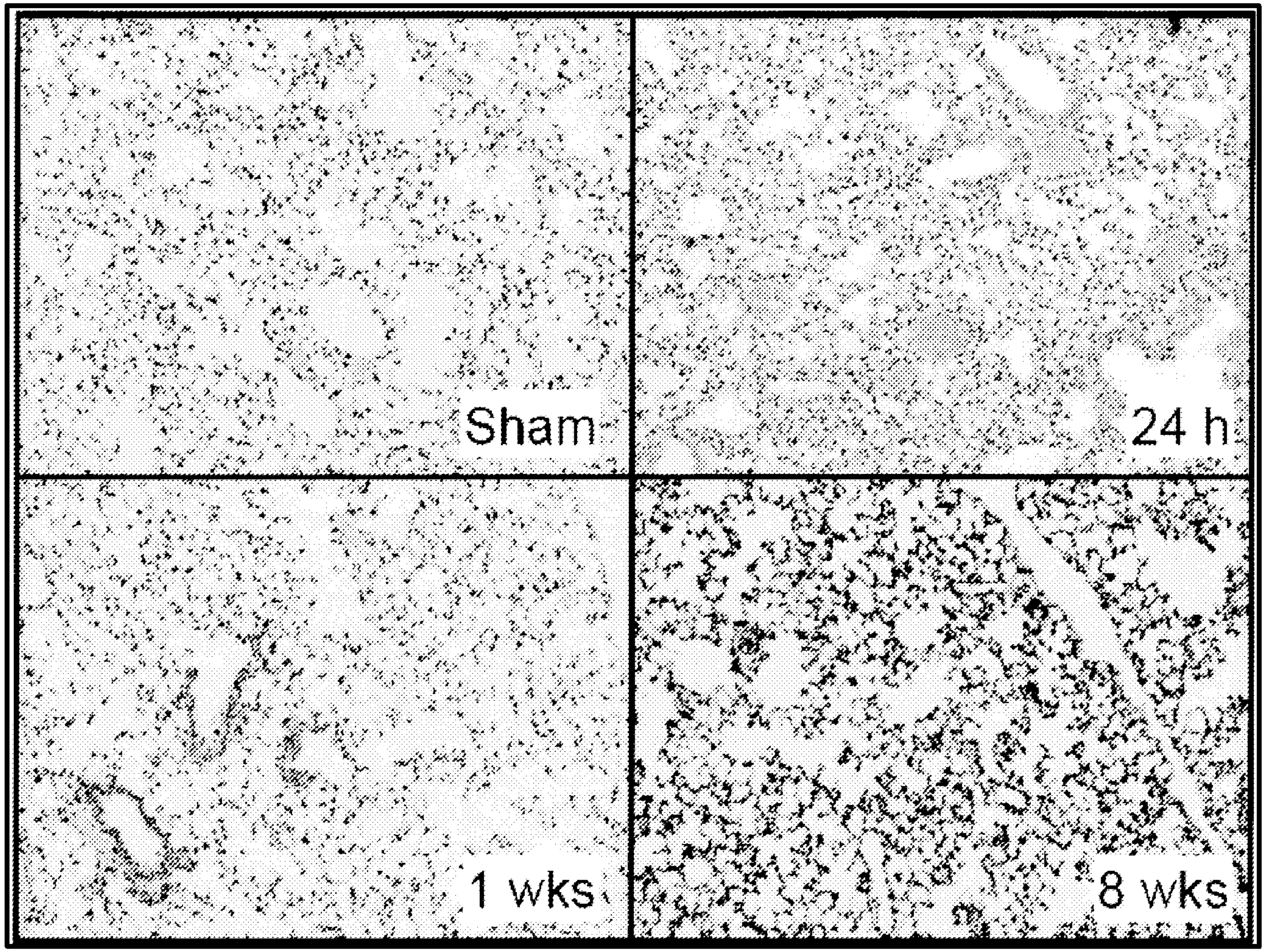


FIG - 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/035230

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 16/00 (2010.01)
USPC - 128/204.17
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) - A61M 16/00 (2010.01)
USPC - 128/203.16, 203.26, 204.15, 204.16, 204.17, 204.18, 204.21, 204.23

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,131,571 A (LAMPOTANG et al) 17 October 2000 (17.10.2000) entire document	1-20
Y	US 2006/0037613 A1 (KWOK et al) 23 February 2006 (23.02.2006) entire document	1-20
A	US 2009/0038615 A1 (BRADLEY) 12 February 2009 (12.02.2009) entire document	1-20
A	US 6,523,538 B1 (WIKEFELDT) 25 February 2003 (25.02.2003) entire document	1-20

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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 28 June 2010	Date of mailing of the international search report 12 JUL 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774