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1. Name of conveying party(ies):
Woodie Roy

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☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Texas Pharmaceuticals, Inc.

Internal Address:

Street Address: 701 W. 4th Street

City: Texarkana

State: TX Zip: 75501

3. Nature of Conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other

Execution Date: July 21, 1998

Additional name(s) & address(es) attached?
☐ Yes ☒ No

4. Application number(s) or patent number(s): PCT/US99/16940

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s):

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: David L. Fox

Internal Address: Fulbright & Jaworski LLP

Street Address: 1301 McKinney

Suite 5100

City: Houston

State: TX Zip: 77010-3095

6. Total number of applications and patents involved: 2

7. Total fee (37 CFR 3.41): . . . . . $ 40.00

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David L. Fox — Name of Person Signing

Signature

17 July 2000 — Date

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Total number of pages including cover sheet, attachments, and document: 8

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

ASSIGNMENT

DATE: July 21, 1998

ASSIGNOR: WOODIE ROY
c/o 701 W. 14th Street
Texarkana, Texas 75501

ASSIGNEE: TEXAS PHARMACEUTICALS, INC., a Texas corporation
701 W. 14th Street
Texarkana, Texas 75501

In consideration of Ten Dollars ($10.00) cash in hand paid to me and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I, WOODIE ROY (hereinafter called "Assignor"), who have made an invention of a novel use and method of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, assign, sell, transfer and convey to TEXAS PHARMACEUTICALS, INC., a Texas corporation, whose address is 1314 Main Street, Texarkana, Bowie County, Texas 75501 (hereinafter called "Assignee"), its successors and assigns, Assignor's entire right, title and interest in and to the following rights, interest, and property (hereinafter collectively called the "Rights"):

1. Assignor's invention of uses, methods and therapies of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, including without limitation Assignor's rights, powers, interests and title in and to the methods, uses and processes described in Schedule 1 attached to this Assignment, (collectively, herein called the "Invention").

2. All applications for patent or like protection on said Invention that have been or may in the future be made by Assignor or Assignor's legal representatives, in any and all countries.

3. All patents and like protection that have been or may in the future be granted on said Invention to Assignor or Assignor's legal representatives, in any and all countries of the world.

4. All substitutions for and divisions, continuations, continuations-in-part, renewals, reissues, extensions and the like of said applications and patents and similar rights or grants, including, without limitation, those obtained or permissible under past, present and future law and statutes.

5. All rights of action on account of past, present and future authorized or unauthorized use of said Invention and for infringement of said patents and like protection.

6. The right of Assignee to file in his name disclosure documents, applications for patents and like protection for said Invention in any country and countries in the world.

7. All international rights of priority associated with said Invention, disclosure filings, applications, patents and like protection.

TO HAVE AND TO HOLD the Rights unto the Assignee, its successors and assigns forever, and Assignor does hereby bind himself, his heirs, legal representatives and assigns, to forever WARRANT and DEFEND the title to the Rights unto the said Assignee, its successors and assigns, against any person whomsoever lawfully claiming, or to claim the same, or any part thereof.

Assignor covenants and agrees that Assignor will cooperate with Assignee such that Assignee may enjoy to the fullest extent the benefit of this Assignment. Such cooperation shall include, but not limited to, all of the following:

1. Assignor's prompt execution of all papers that are deemed necessary or desirable by Assignee to perfect the right, title and

interest herein conveyed, and

2. Assignor's prompt execution of all petitions, oaths, specifications, declarations or other papers that are deemed necessary or desirable by Assignee for filing and prosecuting patent applications, for filing and prosecuting substitute, division, continuing, or additional applications in the United States and/or all foreign countries, for filing and prosecuting applications for reissuance or reexamination of letters patent, and for interference proceedings involving and covering any of the Rights, and

3. Assignor's prompt assistance and cooperation, including but not limited to execution of documents and testifying, in the prosecution of legal proceedings involving any of the Rights, including, but not limited to, patent prosecution, interference proceedings, infringement court actions, opposition proceedings, cancellation proceedings, priority contests, unfair competition court actions, trade secret court actions, public use proceedings, slander, license breach and royalty collection proceedings and other legal proceedings.

Assignor warrants that Assignor has the right to make the assignment set forth herein and that no other person or entity has any rights of ownership or claim to the subject matter of this Assignment as of the date of this Assignment. This Assignment is binding upon Assignor, Assignor's heirs, administrators, executors, successors, trustees, devisees and assigns and inures to and for the benefit of Assignee, its successors and assigns.

EXECUTED effective as of the date first above written and at the time and place indicated below opposite the signature:

Woodie Roy
WOODIE ROY

Date: 7-24-98

STATE OF TEXAS §
§
COUNTY OF BOWIE §

BEFORE ME, the undersigned authority, on this day personally appeared WOODIE ROY known to me to be the person whose name is subscribed to the foregoing instrument, and acknowledged to me that she executed the same for the purposes and consideration therein expressed.

GIVEN UNDER MY HAND AND SEAL OF OFFICE, this the 24th day of July, 1998.

Patricia M. Reynolds
Notary Public Signature

(SEAL)

PATRICIA M. REYNOLDS
NOTARY PUBLIC
STATE OF TEXAS
My Commission Expires 09-09-99

PATRICIA M. REYNOLDS
Notary Printed Name

Commission Expires: 9/9/99

SCHEDULE 1 TO ASSIGNMENT

INVENTION

This invention provides a medical method for: (1) prevention of life threatening hypothermia; (2) enhancing magnetic resonance spectroscopy and positron emission tomographic metabolic imaging; and (3) treatment of resistant neoplastic and infectious disease by concurrent administration of dinitrophenol [or other mitochondrial thermoregulatory uncoupling agents, e.g., carbonylcyanide m-chorophenylhydrazone (CCCP), carbonylcyanide-p-trifluoromethoxy-phenylhydrazone (FCCP), recombinant brown fat type protein, or lipid proton ionophores] and respiratory oxygen, intravenous fluids, anti-platelet drugs, as needed cooling, and specific metabolic, activating cytokines [e.g., recombinant tumor necrosis factor (TNF), interferons, etc.], hormones (e.g., glucagon), and other medications to control and focally enhance the mitochondrial uncoupling effects.

The present invention avoids the use of labor intensive, complex hyperthermia equipment, including invasive extracorporeal perfusion, with its associated thermal gradient toxicity problems to interposed normal tissues, inherent to all therapeutic methods of delivering heat from the outside-in. A new use(s)/method of generating intracellular oxygen derived free radicals, and heating from within the cell has been discovered for dinitrophenol (or other oxidative phosphorylation uncouplers) in prevention of cold injury, and treatment of free radical-thermosensitive parasites (e.g., Echinococcus), bacteria (e.g., Borrelia burgdorferi), lipid enveloped viruses (e.g., HIV), and neoplasia (e.g., gastric adenocarcinoma). It has further been discovered that cataracts, induced by dinitrophenol in the treatment of chronic obesity, can be prevented by concomitant administration of a variety of free radical scavenging agents, including tocopherol, ascorbic acid, and beta-carotene.

Briefly, the present invention is a new use(s)/method of inducing increased, intracellular free radical flux and hyperthermia, including the procedure of administrating dinitrophenol to patients in doses sufficient to denature and inactivate targeted biologic systems. Concurrent administration of tissue selective activating hormones, biologicals or drugs permits greater enhancement of the therapeutic index, while physiologic gain cooling, fluids, respiratory oxygen, and monitoring procedures permit safe therapeutic control. The figure on the attached page depicts an example use(s)/methodology of this process in an algorithm.

SCHEMATIZED MITOCHONDRIAL UNCOUPLING METHOD FOR DIAGNOSIS OR TREATMENT OF INFECTIOUS AND MALIGNANT DISEASE

ORGANISM or MALIGNANCY

PATIENT

TREATMENT EVALUATION

BIOLOGIC CRITERIA

* Confirmed Diagnosis by culture, PCR, or histopathology; specific serology.
* Known Temperature and Heating Time required for inactivation, e.g., Treponema pallidum (syphilis)-41.5°C @ 1 hour; Borrelia burgdorferi (Lyme Disease)-41.5°C @ 1 hour; Echinococcus multilocularis (Hydatid infestation)-41°C @ 15 minutes; HIV, chronically infected (provirus) cells (tissue culture)-42°C @ 10 hours, with recombinant TNF-a, 42°C @ 3 hours. Kaposi's sarcoma, HIV infection in the patient-42°C @ 2 hours/44°C @ 15 minutes.
* Unknown Temperature and Heating Time required for inactivation of neoplasms, or other infectious agents, determined by predictive - assay of biopsy/culture; generally, treatment temperature/time will be decreased due to endogenous uncoupling also occurring in targeted biologic system (except viral).

CLINICAL CRITERIA

* History of cardiac, hepatic, pulmonary renal, CNS, malignant hyperthermia, or endocrine disease, i.e., exclusion of patients-congestive heart failure, severe dysrhythmias; alcoholic or other hepatitis with elevated bilirubin/enzymes; known endocrinopathies of brittle diabetes, pheochromocytoma, etc.; medications known to stimulate the physiologic response of hypermetabolic state and hyperthermia, e.g., vascular constrictors, anticholinergics, calcium channel blocker, etc.
* Pulmonary, renal, hepatic function tests; chest X-ray; CBC with platelet count; Chem profile with Ca^{++}, Mg^{++}, $PO_4^{=}$; exercise-multigated cardiac radionucleotide scan with resting ejection fraction of at least 45%, and no deterioration upon exercise.
* Enhancing or sensitizing agents to increase therapeutic gain, i.e., use of ionizing radiation, chemotherapy, drugs, or biologic modifiers (synergistic or additive).

METHOD PROTOCOL

TREATMENT

* Dinitrophenol, dosage & schedule on "Biologic/Clinical Criteria"; IV (or IM-SC) test dose (1mg/kg) by VO_2 response-1ml O_2/sec=20watts; common IV dosage, 1-5mg/kg, q 1-4 hr, PO 2X greater q 6-12 hr; BMR & heat dissipation modify dose/schedule.
* Other mitochondrial uncoupling agents, increased potency/more localized effect, e.g., FCCP, CCCP, perfluorooctane sulfonamide, SF-6847; long chain fatty acids, and brown fat "thermogin", etc.
* Modulating-controlling agents, tissue specific mediators which modulate substrate turnover rates through Krebs cycle; glucagon, .5-10mg/hr-IV; dopamine(1-10 micrograms/kg/min); insulin-dose based on blood glucose; dobutamine(1-15 micrograms/kg/min); amrinone(5-7.5 micrograms/kg/min); isoproterenol (.5-2 micrograms/min).

BASELINE & MONITORED

* Oxygen consumption/increase, precedes core temperature increase by 4 minutes; prolonged or high risk patient-additional monitoring of tissue oxygenation by gastric pH, NMR, PET or infrared spectroscopy, ear oximetry, blood gas.
* Core temperature, esophageal, rectal, bladder catheter thermistors.
* Cardiac function, continous display of rhythm, rate, blood pressure and respiratory rate; Swan-Ganz catheter for high risk patient.
* Renal output/function, maintain at least 1-1.5ml per kg/hour; observe for possible myoglobinuria and monitor fluid input/output.
* Hepatic function tests, at target temperature; isoenzyme fractionation if tumor lysis is a consideration.
* CNS agitation, anxiety, possible seizure prophylaxis.
* Blood chemistry/electrolytes-glucose, $PO_4^{=}$, serum creatinine.

MANAGEMENT

* Oxygen (100%) @ 4-6 liters/minute via nasal cannula/face mask.
* Heat control with evaporation preventing-water absorbing blankets/plastic liners; cooling control-if needed with tepid H_2O spray and/or fan evaporative loss; use of P.O. propylthiouracil (PTU); Decadron-I.V.
* Intravenous fluids, i.e., .85% Saline, D_5W-$\frac{1}{2}$NS, supplemented with appropriate milliequivalents of K^+, $PO_4^{=}$, Mg^{++}; fluid rate to compensate for evaporative and urinary losses, maintain BP.
* Arrhythmia control, if needed-use of non-negative inotropic, or drugs that cannot cause cardiac decompensation in hypermetabolic state e.g., lidocaine; avoidance of beta blockers and Ca^{++} channel blockers.
* Anxiety, possible seizure control with I.V. valium, thiopental; avoidance of drugs with atropine like effects or major anti-psychotic drugs.

MEDICAL USES

DNP-IV @ 1mg/kg (2X-VO_2) → DIAGNOSIS - Enhancement of NMR, PET, & Near-Infrared Spectroscopy. → Sensitivity increased by enhanced metabolic differences between diseased/normal tissues, i.e., O_2, glucose, fatty acid, ATP, phosphocreatine & specific substrate consumption; lactic acid, free radical production; early diagnosis & predictability of disease treatment parameters/success

DNP-IV @ 2-5mg/kg q3-6hr for 2X-VO_2 → THERAPY OF INFECTIOUS & MALIGNANT DISEASE (dosage/frequency of uncoupling agent will be determined by the specific agent treated & use of modulating, enhancing, or other combined therapy drugs.

- → PARASITIC (See Illustrative Example)
- 41.5°C/1 hr (or less) → BACTERIAL (Borrelia burgdorferi)
- 42°C/2 to 8 hrs (or less) → VIRAL (HIV)
- Based on predictive biopsy and use of radiation, chemotherapy or biologic response modifiers → NEOPLASTIC

PATENT
REEL: 012063 FRAME: 0029

ILLUSTRATIVE METHOD/USE EXAMPLE [1/]

A 52 year old white Swiss male, hunting dog trainer, presented with right upper quadrant abdominal pain. History revealed past(24 month old) hepatic "cyst" surgery and treatment with albendazole(only 1 dose was given because of anaphylactic reaction). He denied history of weight loss, pulmonary, cardiac or neurologic disease. Upon physical examination, he had a weight of 198 pounds (90 Kg), height of 5'11", blood pressure 140/80, pulse-76 and regular, respirations 18/minute, and oral temperature of 37.3°C. Laboratory studies, including hepatic, renal, pulmonary and cardiac function tests were normal; complete blood count was unremarkable except for 20% eosinophilia. Ultrasound and nuclear magnetic resonance of the liver revealed 4 (2-3 cm. in diameter) cysts in the mid-right lobe; ELISA serology showed a diagnostic titer specific for Hydatid disease with Echinococcus multilocularis. The patient refused to entertain any additional surgery or albendazole therapy.

After clinical assessment and treatment evaluation, i.e., Echinococcus multilocularis protoscoleces and germinal layers are destroyed at 41°C/15 minutes, whereas liver-hepatocytes withstand temperatures of 42°C to 44°C for known periods of 20 hours and 15 minutes respectively, the patient was given 1 aspirin; 10 mg. diazepam by mouth; and, intravenous fluids of 0.85 normal saline containing 9 millimolar K_2PO_4, 7 milliequivalents of K^+, and 2cc of 50% saturated solution of Mg_2SO_4/liter, were infused at a rate of 12cc/kg/hr. Urine output was maintained at 1cc/kg/hour or greater. Esophageal (optional), rectal and foley (16 gauge) tipped bladder catheter thermistors gave temperature readings every two minutes within 0.1°C. Cardiac rate, rhythm, blood pressure, and repiratory rate sensors were placed and continously displayed on a multichannel monitor. Intravenous glucagon-2mg/hr was infused, with 1 mg given prior to DNP.

The patient was covered with a water absorbing polyethelene lined blanket, and baseline respiratory gas flow/oxygen consumption (VO_2) was determined using a 3 minute bag collection. Five minutes after intravenous administration of 90 mg of dinitrophenol (2% DNP/5% $NaHCO_3$ at 1 mg/kg), and determination that there was no untoward or idiosyncratic reaction, an additional 90 mg of 2,4 dinitrophenol (total of 180mg, 2mg/kg body weight) was infused. Monitored physiologic parameters are shown in the Table below. An additional VO_2 rate was obtained five minutes after the second dose of DNP and the patient was thereafter placed on 100% O_2 via nasal canula. Target core temperature was maintained by occasional exposure of a limb and/or decreasing the glucagon infusion rate to 0.25 mg/hour. After the patient was maintained at a core temperature of 41.3°C for 20 minutes, the treatment was terminated by removing the blanket and permitting evaporative and radiant heat loss to return the body temperature to a normothermic level.

TABLE

Monitored Clinical Data On Mitochoodrial Uncoupling Use/Method In Illustrative Example
(Treatment of Hydatid disease-Echinococcus multilocularis)

Time (minutes)	Medication (type & dose)	Resp. Rate	O_2 Consumption (ml/min)	Cardiac Rate (beats/min)	Urine Output (total ml)	Core Temp. (°C)	Other (remarks)
-60	I.V. Fluids - .85% NS @ 0.8 L/hour	18	290	78	-	37.1	Fluids @ 10-12cc per kg/hour.
-30	Glucagon-IV Drip @ 2mg/hour	20	-	78	47	37.1	Hepatic Krebs Cycle stimulation.
0	2,4-dinitrophenol-90mg IV in 4.5ml of 5%$NaHCO_3$ [prepared by dissolving 2.3gm DNP(15% H_2O) in 5% $NaHCO_3$-giving 2% solution]	20	-	88	58	37.4	Covered with polyethylene blanket.
2		24	350	92	-	37.8	Increased O_2 consumption precedes temp. elevation.
5	2,4-dinitrophenol-90mg IV in 4.5ml of 5%$NaHCO_3$	26	-	98	-	37.8	
10	Fluids increased to 1.2 L/hour; start O_2	30	630	110	15	39.4	After VO_2 determined 100% O_2 @ 4 L/min via nasal cannula.
20	-	30	-	120	18	40.3	
40	Glucagon -IV Drip decreased to 0.5mg/hr	30	-	138	25	41.4	Lower extremity is partially exposed.
60	Glucagon discontinued	30	-	140	30	41.2	Blanket removed
120	IV fluid discontinued	24	-	100	98	38.4	All thermistors removed

1/ Variations of the above use/method, i.e., protocol evaluation, monitoring, medications/dosages, time & temperature of mitochondrial uncoupling, will be necessitated by clinical and targeted biologic system treatment factors. Such variations for treatment of other parasitic (e.g. Malaria), bacterial (e.g., Lyme, Hansens disease), viral (e.g., HIV) and neoplastic disease will occur to those skilled in the art of medicine, and will be more fully described in the patent application.