

09-16-2003

Attorney Docket No. 19705-029



102551697

FORM PTO-1595

RECORDA  
OFFICE OF PUBLIC RECORDS

2003 SEP 11 AM 10:48

U.S. DEPARTMENT OF COMMERCE  
Patent and Trademark Office

**FINANCE SECTION** Please retain the attached original documents or copy thereof.

1. Name of conveying party(ies):

Albany Medical College

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☐ Assignment ☐ Merger  
☐ Security Agreement ☐ Change of Name  
☒ Other: Research Agreement and modifications thereto. Please note that this recordation also intends to clarify the earlier conveyance between Davis and Albany Medical College, which is recorded at Reel/Frame 013053/0914. The present Research Agreement was already in force and gave rights to CLFMTAP at the time of the earlier conveyance. Dr. Davis' work under the Research Agreement was subject to the Patent Policies of AMC, as noted in the Agreement. Therefore, the conveyance from Davis to AMC should be disregarded when considering record chain of title.

2. Name and address of receiving party(ies)

Name: Charitable Leadership Foundation – Medical Technology Acceleration Program

Internal Address: 747 Pierce Road, Clifton Park, NY 12065

Street Address: 747 Pierce Road, Clifton Park, NY 12065

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

4. Application number(s) or patent number(s):

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

A. Patent Application No(s):

10/146,566

B. Patent No(s):

Additional numbers attached? ☐ Yes ☒ No

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

Name: Ivor R. Elrifi  
Address: MINTZ, LEVIN, COHN, FERRIS  
GLOVSKY and POPEO, P.C.  
One Financial Center  
Boston, MA 02111

6. Total number of applications and patents involved: [ 1 ]

7. Total fee (37 CFR 3.41)

\$40.00

- ☒ Enclosed  
☒ The Commissioner is authorized to charge Deposit Account  
No: 50-0311, Reference No. 19705-029

DO NOT USE THIS SPACE

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.

Nicholas P. Triano III, Reg No. 36,397

September 11, 2003

Name of Person Signing

Signature

Date

Total number of pages including cover sheet, attachments, and document: [ 25 ]

Mail documents to be recorded with required cover sheet information to:

MAIL STOP ASSIGNMENT RECORDATION SERVICES  
Director of the U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

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PATENT  
REEL: 014483 FRAME: 0816

MAY. 28. 2003 10:39AM

NO. 804 P. 1

**RESEARCH AGREEMENT**

This agreement, made this 24th day of January, 2000 by and between ALBANY MEDICAL COLLEGE with offices located at 47 New Scotland Avenue, Albany, NY 12208, hereinafter referred to as "College", a private not-for-profit corporation, and Northern California Institute for Research and Education, Inc., hereinafter referred to as the "Contractor".

**WHEREAS**, the College has been awarded a grant from the Charitable Leadership Foundation, hereinafter referred to as the "Sponsor", and

**WHEREAS**, part of the overall project involves the following: "Rescue of hypoxic kidney and muscle cells with pyrroloquinoline quinone (PQQ)", and,

**WHEREAS**, the Contractor has represented to the College that it is knowledgeable, qualified, and experienced in the skill(s) required for this project, and that it is willing and capable of performing the services required hereunder

Now, therefore, in consideration of the promises and mutual covenants herein, the parties agree as follows:

**Definitions:** Throughout this agreement, the following terms shall have the following definitions:

"Contract Start Date": February 1, 2001 "Contract End Date": March 31, 2002

"Total Contract Amount": \$ 25,000

"College Project Director": Paul J. Davis, M.D.

"Required Voucher Frequency": Quarterly (beginning June 30, 2001)

"College Reference Number": 302102

"Budget Flexibility Percentage": Not Applicable

**Attachments / Exhibits:** The following are hereby incorporated and made part of this agreement:

Exhibit A: *Scope of Work*

Exhibit B: *Budget*

Exhibit C: *Sample Voucher and Reporting Instructions*

Attachment A: *General Terms and Conditions for College Contracts*

Attachment B: *Program Specific Clauses and/or Certifications*

IN WITNESS WHEREOF, this Agreement has been duly executed by the parties hereto as the date first above set forth.

Albany Medical College

James E. Peterson, Ph.D.

Director of Research Administration

Contractor

Name: Jack Negan

Title: Chief Executive Officer

Tax ID Number: 1943066159A1

**ATTACHMENT A**  
**GENERAL TERMS AND CONDITIONS**  
**ALBANY MEDICAL COLLEGE CONTRACTS**

1. **PERIOD OF PERFORMANCE:** The period of performance, including specifically the incurrence of allowable costs, may not be changed except by modification to this Agreement.
2. **SCOPE OF WORK AND KEY PERSONNEL:** The Contractor agrees to furnish and deliver the supplies and perform the services set forth in this Agreement for the consideration stated herein.

The Contractor shall provide the necessary personnel, equipment, facilities, and supplies to accomplish the research tasks as set forth in the attached Scope of Work (Exhibit A). The Scope of Work may not be changed without the prior written approval of the College.

In order to assure a well-integrated research effort, the Contractor agrees, for itself and its agents and employees, that it will at all times during the performance of this Agreement maintain close liaison with the College's indicated project director. All services provided for herein shall be performed as directed by and to the approval of the College's project director.

The Contractor shall not replace its project director without the prior written approval of the College.

3. **ALLOWABLE COSTS:** For the purpose of determining the amounts payable to the Contractor under this Agreement, the allowability of costs shall be determined in accordance with (1) the terms of this Agreement, (2) the budget (Exhibit B).
4. **LIMITATION ON COSTS:** The costs of performing the tasks under Scope of Work (Exhibit A) shall not exceed the Budget (Exhibit B). The College is not, in the absence of a modification to this Agreement, obligated to reimburse the Contractor for costs incurred by the Contractor which are in excess of the cost specified in Exhibit B.
5. **REBUDGETING:** This Agreement may be changed, amended, modified or extended only by mutual consent provided that such consent shall be in writing and executed by the parties hereto prior to the time such change shall take effect. The Budget Flexibility Percentage indicates the percent change allowable in each category of the Budget. As with any desired change to this Agreement, budget category deviations exceeding the Budget Flexibility Percentage in any category of the Budget are not permitted unless approved in writing by the College. In no way shall the Budget Flexibility Percentage be construed to allow the contractor to exceed the Total Contract Amount, nor shall it be construed to permit charging of any unallowable expense to any budget category. An otherwise allowable charge is disallowed if the charge amount plus any Budget Flexibility Percentage exceeds the amount of the budget category for that cost.  
  
Rebudgeting between budget categories on the part of the Contractor will be in accordance with the terms of this Agreement as stated on page 1.
6. **PAYMENTS:** The Contractor shall submit voucher claims (Exhibit C) and reports of expenditures at the Required Voucher Frequency noted on the face page of this Agreement, in such form and manner as the College shall require. The College will reimburse Contractor upon receipt of expense vouchers pursuant to the Budget in Exhibit B, so long as Contractor has adhered to all the terms of this Agreement and provided the reimbursement is not disallowed or disallowable under the terms of this Agreement. All information required on the voucher must be provided or the College may pay or disallow the costs at its discretion. The College reserves the right to request additional back up documentation on any voucher submitted. Further, all vouchers must be received within thirty (30) days of the end of each period defined as the Required

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NO. 804 P. 3

Voucher Frequency (i.e. each month, each quarter). Contractor shall submit a final voucher designated by the Contractor as the "Final Voucher" no later than fifteen (15) days from termination of the Agreement.

The Contractor represents, warrants and certifies that reimbursement claimed by the Contractor under this Agreement shall not duplicate reimbursement received from other sources including, but not limited to client fees, private insurance, public donations, grants, legislative funding from units of government, or any other source. The terms of this paragraph shall be deemed continuing representations upon which the College has relied in entering into and which are the essence of its agreements herein.

7. **INDEPENDENT CONTRACTOR:** Contractor is an independent contractor, not a partner, joint venturer, or agent of the College; nor are the Contractor's employees considered employees of the College for any reason.
8. **REPORTS:** The Contractor is responsible to the College for the submission of timely and complete reports as required under the terms and conditions of the grant and to the satisfaction of the project director of the College.
9. **PUBLICATIONS:** All written materials, publications, audio visuals that are either presentations of, or products of the Scope of Work will credit Albany Medical College and the Project Sponsor and will specifically reference the Sponsor Reference Number as the contract/grant funding the work. This requirements shall be in addition to any publication requirements or provisions specified in Attachment B - Program Specific Clauses.
10. **PATENTS AND INVENTIONS:** This Agreement is subject, when applicable, to the Patent Policy of the Albany Medical College and applicable provisions of Project Sponsor policies on patents and inventions. Disposition of patent rights shall be determined in accordance with the aforesaid policies. The Contractor agrees that the Standard Patent Rights Clauses (37 CFR 401.14) are hereby incorporated by reference to the extent applicable by law or regulation.
11. **INDEMNIFICATION:** Contractor agrees (a) to maintain contractual obligations insurance covering this Agreement if requested; (b) to maintain all statutory workers compensation and disability insurance for himself/herself as is required by law, and for all employees; and (c) to indemnify, defend and hold College harmless from and against any and all liabilities arising from injuries (including death) to himself/herself and any and all persons employed by Contractor in performance of this agreement and from and against any and all liabilities for injury (including death) to any persons, or injury to property, in any manner resulting from or caused by performance of this Agreement or any portion hereof, except only such liability as may be determined by a court of competent jurisdiction to have arisen solely from the negligence of the College. Similarly, College agrees to indemnify, defend and hold Contractor harmless from and against any and all liabilities arising from injuries (including death) to himself/herself and any and all persons employed by College in performance of this Agreement and from and against any and all liabilities for injury (including death) to any persons, or injury to property, in any manner resulting from or caused by performance of this Agreement or any portion thereof, except only such liability as may be determined by a court of competent jurisdiction to have arisen solely from the negligence of Contractor.
12. **LIABILITY TO THIRD PARTIES:** Contractor agrees that it will be solely liable for any and all claims of any third parties for damages, and expenses of whatsoever nature arising from, growing out of, or related to the Contractor's performance or failure to perform pursuant to this Agreement and that Contractor shall hold College harmless from any such claims or damages.
13. **ASSIGNMENT AND SUBCONTRACTING:** The Contractor shall not assign, transfer or convey this Agreement or any part hereof, or any interest herein, nor shall the Contractor contract for the performance

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of any of its obligations hereunder, without the prior written consent to the College. Any such contracts and all other arrangements made by the Contractor in connection with its performance hereunder, including Contractor's arrangements with its agents and employees, shall be made subject to, and consistent with the conditions, and limitations of this Agreement and adequately ensure the subcontractor's compliance including indemnification of the College.

14. **TERMINATION:** This Agreement may be terminated without cause by the College upon thirty (30) days' written notice. In addition, the College may terminate this contract immediately in the event of a material breach by Contractor. The College will notify the Contractor in writing in the event that the agreement is terminated. In the event of such termination, the Contractor shall immediately discontinue all work and services under this Agreement and shall take steps as are necessary to terminate any and all obligations which it may have entered into and shall, with the approval and ratification of the College, settle all outstanding liabilities and claims resulting from such termination.

The Contractor may terminate this Agreement upon thirty (30) days' written notice to the College.

15. **USE OF NAME:** Contractor agrees not to use the name of the Albany Medical College, or any staff members or employees thereof, in advertising, sales promotion work, or in any other form of publicity except with the written permission of, and to the extent approved by the Albany Medical College.

Albany Medical College agrees not to use the name of Contractor, or any staff members or employees thereof, in advertising, sales promotion work, or in any other form of publicity except with the written permission of, and to the extent approved by Contractor.

16. **AMENDMENTS:** This Agreement may be changed, amended, modified or extended only by a writing duly executed by the respective parties hereto.

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**ATTACHMENT B**  
**PROGRAM SPECIFIC CLAUSES AND/OR CERTIFICATIONS**  
**ALBANY MEDICAL COLLEGE CONTRACTS**

**ASSURANCES**

Contractor agrees to the extent required under the College's agreement with the Project Sponsor that it will comply with the following provisions:

**(a) Protection of Human Subjects**

Should human subjects be used in this project, the Contractor will comply with DHHS policies and regulations on the protection of human subjects (45 CFR 46, as amended). In addition to assuring that the initial requirements for the protection of human subjects are met, the Contractor agrees to assure continued monitoring and compliance with these requirements during the course of this project. A copy of HHS 310 Form or a letter from the IRB Chairman, indicating the date that the project was reviewed and approved, must be submitted to the College. The Contractor assures the College that it has valid Assurances of Compliance on file with DHHS.

**(b) Humane Care and Treatment of Animals**

Should warm-blooded animals be used in this project, the Contractor will comply with the applicable portions of the Animal Welfare Act (P.L. 89-544, as amended), and will follow the guidelines prescribed in DHHS Publication No. 72-23 (NIH) "Guide for the Care and Use of Laboratory Animals", and any other applicable Federal and/or State regulations. A copy of the Institutional Animal Care and Use Committee approval letter, indicating the date that the project was reviewed and approved, must be submitted to the College. The Contractor assures the College that it has valid Assurances of Compliance on file with DHHS.

**(c) Civil Rights and Equal Employment Opportunity**

The Contractor will comply with Title VI of the Civil Rights Act of 1964, and Section 504 of the Rehabilitation Act of 1973, as amended. The Contractor assures the College that it has valid Assurances of Compliance on file with DHHS.

**(d) Student Unrest Provisions**

The Contractor will be responsible for carrying out the provisions relating to remuneration from project funds to any individual who has been engaged or involved in activities described as "student unrest". (Section 407 of the DHHS Appropriations Act each year since FY 1970.)

**(e) Debarment and Suspension**

In accepting this Agreement, the Contractor certifies that neither it nor its principals are presently debarred, suspended, proposed for debarment, declared ineligible or voluntarily excluded from participation in this transaction by any Federal department or agency. Any change in the debarred or suspended status of the Contractor during the life of this Agreement must be report immediately to the College. The Contractor agrees to incorporate the Debarment and Suspension certification into any subgrant that they may enter into as a part of this Agreement.

This certification is required by the regulations implementing Executive Order 12549, Debarment and Suspension, 34 CFR Part 85, Section 85.510, Participant's responsibilities. The regulations were published as Part VII of the May 26, 1988 Federal Register (pages 19160-19211). If the Contractor is unable to certify to any of the statements in this certification, the Contractor shall attach an explanation to this Agreement.

**(f) Non-Delinquency on Federal Debt**

Contractor certifies that it is not delinquent on the repayment of any Federal debt(s) (OMB Circular A-129, November 25, 1988).

**(g) Certification of Drug Free Workplace**

Contractor certifies that it will comply the Drug-Free Workplace Act of 1988 (45 CFR Part 76, Subpart F and Federal Register, January 31, 1989).

**(h) Certification Regarding Lobbying**

Contractor certifies that it will comply with the Office of Management and Budget, DHHS, interim final guidance on lobbying (Federal Register Vol. 54, No. 243, December 20, 1989) and Section 319 of the U.S. Code, signed into law on October 23, 1989), assuring that no federally appropriated funds have been paid or will be paid for lobbying. If this Agreement exceeds \$100,000, Contractor must submit DHHS "Certification Regarding Lobbying" to College. If any funds other than Federal appropriated funds have been paid or will be paid for lobbying, the Contractor will submit Standard Form LLL "Disclosure Form to Report Lobbying Activities" to the College.

**(i) Misconduct in Science**

Each institution which receives or applies for a research, research-training, or research-related grant or cooperative agreement under the Public Health Service Act must submit an annual assurance certifying that the institution has established administrative policies as required by the Final Rule (42 CFR Part 50, Subpart A), and that it will comply with those policies and the requirements of the Final Rule as published at 54 FR 32446, August 8, 1989.

In accepting this Agreement, the Contractor certifies that it has: (1) established, and will comply with, policies and procedures, incorporating the provisions set out in 42 CFR Part 50 for inquiring into and investigating allegations of scientific misconduct, and otherwise comply with 42 CFR 50.101-50.105; (2) will comply with the requirements of the PHS regulations on responsibilities of awardee and applicant institutions for dealing with and reporting possible misconduct in science (42 CFR Part 50, Subpart A); and (3) will provide its policies and procedures to the Public Health Service upon request.

Contractor will submit to College a copy of its most recent assurance for dealing with and reporting possible misconduct in science which has been filed with the Office of Scientific Integrity, PHS.

**(j) Use of Recombinant DNA**

If this Agreement involves Recombinant DNA research, the Contractor agree to refer to the relevant provisions of the most recent guidance from NIH concerning Recombinant DNA research to determine the requirements necessary for the preparation of application involving Recombinant DNA experiments.

**(k) Conflict of Interest**

The Contractor will comply with DHHS policies and regulations prescribed by 45 CFR Part 74, Subpart P, 45 CFR Part 92.36, and NIH Grants Policy Statement (effective 10/1/98).

**(l) Safety and Health Clauses**

The Contractor agrees to comply fully with state and federal safety and health regulations that apply to the performance of this Agreement.

- (m) **Investigator Significant Financial Interest Disclosure Policy**  
The Contractor will comply with 42 CFR Part 50 and 42 CFR Part 64, and will assure Albany Medical College that any significant financial interest will be managed, reduced, or eliminated for any investigator (including spouses and dependent children) involved in this project at the Contractor's site.
- (n) **Age Discrimination Act of 1975**  
The Contractor will comply with the Age Discrimination Act of 1975 (P.L. 94-135) as amended, as implemented by 45 CFR 1.
- (o) **Title IX of the Education Amendments of 1972**  
The Contractor shall comply with Title IX of the Education Amendments of 1972, in particular section 901 as implemented at 45 CFR Part 86 (elimination of sex discrimination).
- (p) **Non-Discrimination for Drug/Alcohol Abusers in Admission or Treatment**  
The Contractor shall comply with Sections 522 and 526 of the PHS Act as amended, implemented at 45 CFR Part 84.
- (q) **Confidentiality of Records of Substance Abuse Patients**  
The Contractor shall comply with Section 543 of the PHS Act as amended as implemented at 42 CFR Part 2.
- (r) **Americans With Disabilities Act of 1990**  
The Contractor shall comply with the Americans with Disabilities Act of 1990, 42 USC 12132 ("ADA"), and regulations promulgated pursuant thereto, see 28 CFR Part 35. The Contractor shall not discriminate against an individual with a disability, as defined in the ADA, in providing services, programs or activities pursuant to this Agreement.
- (s) **Notice as Required Under Public Law 103-333 (American-made)**  
If the Project sponsor is an agency of the Department of Health and Human Services, the Contractor is hereby notified of the following statement made by Congress at Section 507(a) of Public Law 103-333 (The DHHS Appropriations Act, 1995, hereinafter the "Act"): "It is the sense of the Congress that, to the greatest extent practicable, all equipment and products purchased with funds made available in this Act should be American-made."
- (t) **Insurance**  
The Contractor shall maintain or cause to be maintained, through the term of this Agreement, insurance of the types and in the amounts specified below. It is expressly understood that the coverages and limits referred to herein shall not in any way limit the liability of the Contractor. The Contractor shall include a provision in all subcontracts requiring the subcontractor to maintain the same types and amounts of insurance specified below.
- Workers Compensation for all employees of the Contractor and Subcontractors engaged in performing this Agreement, as required by applicable laws.
  - Disability insurance for all employees of the Contractor engaged in performing this agreement, as required by applicable laws.
  - Employer's liability or similar insurance for damages arising from bodily injury, by accident or disease, including death at any time resulting therefrom, sustained by employees of the Contractor or subcontractors while engaged in performing this Agreement.

- Commercial General Liability insurance for bodily injury, sickness or disease, including death, property damage liability and personal injury liability with limits as follows:
- Each Occurrence - \$1,000,000
- Personal and Advertising Injury - \$1,000,000
- General Aggregate - \$2,000,000
- If hired or non-owned motor vehicles are used by the Contractor in the performance of this Agreement, hired and non-owned automobile liability insurance with a combined single limit of liability of \$1,000,000.
- If contractor uses its own motor vehicles in the performance of the Agreement, Automobile Liability insurance covering any auto with combined single limit liability of \$1,000,000.
- Professional Liability insurance with limits of liability of \$1,000,000 each occurrence and \$3,000,000 aggregate.

**EXHIBIT A**

**SCOPE OF WORK**

Dr. Karliner is a research cardiologist who has established the working Langendorff preparation in his laboratory at the San Francisco Veterans Medical Center. This is an isolated, perfused rat or mouse model in which the organ pumps against a pressure head. In the work to be carried out, a series of hearts will be rendered hypoxic with and without treatment with pyrroloquinoline quinone (PQQ) treatment. To be determined are the effects of PQQ in protecting heart tissue from hypoxic damage and damage due to hypoxia/reperfusion injury. To be monitored are heart rate, rhythm, cardiac work and myocardial enzyme release.

**EXHIBIT B**

**BUDGET**

**Direct Costs Only**

**. 25,000**

**EXHIBIT C**  
**SAMPLE VOUCHER**

**Contractor's Address:**

**AMC REF #:**  
**Prepared:**  
**Contractor #:**  
**Voucher #:**  
**Total Award:**  
**Fed Tax ID:**

**REPORT OF EXPENDITURES FOR THE PERIOD:** \_\_\_\_\_

<b>CATEGORY</b>	<b>CURRENT EXPENSE</b>	<b>CUMULATIVE EXPENSE</b>
Salary	_____	_____
Fringe Benefits @ _____ %	_____	_____
Contractual/Consultant	_____	_____
Staff Travel	_____	_____
Supplies	_____	_____
Equipment	_____	_____
Other Expenses	_____	_____
Total Direct Costs	_____	_____
OVERHEAD @ _____ %	_____	_____
TOTAL EXPENSE @ ____/____/____	_____	_____

**"I certify that all expenditures reported (or payment requested) are for appropriate purposes and in accordance with the provisions of this Agreement."**

**Approved By:** \_\_\_\_\_

**Please mail remittance to:**

**EXHIBIT C**  
**VOUCHER REPORTING INSTRUCTIONS**

Payments for performance under this Agreement shall be made on a Cost-Reimbursement basis. The Contractor shall submit detailed voucher claims on Contractor's letterhead (sample voucher attached) and reports of expenditures at the Required Voucher Frequency noted on the face page of this Agreement, in such form and manner as the College shall require. The College will reimburse Contractor upon receipt of expense vouchers pursuant to the Budget (Exhibit B), so long as Contractor has adhered to all the terms of this Agreement and provided the reimbursement is not disallowed or disallowable under the terms of this Agreement. All information required on the voucher must be provided or the College may pay or disallow the costs at its discretion. The College reserves the right to request additional back up documentation on any voucher submitted. Further, all vouchers must be received within thirty (30) days of the end of each period defined as the Required Voucher Frequency (i.e. each month, each quarter). Vouchers received after the 30 day period may be paid or disallowed at the discretion of the College. Contractor shall submit a final voucher designated by the Contractor as the "Final Voucher" no later than sixty (60) days from termination of the Agreement.

Vouchers shall be submitted to:

Albany Medical College  
Clinical Research Initiative,  
47 New Scotland Ave.  
Albany, NY 12208  
Attn: Kristen Finne

Invoices shall indicate costs, as applicable, to the following categories:

Cost Category  
Salaries and Wages

Required Detail  
The employee's name and the period worked.

Fringe Benefits  
Contractual/Consultant,  
Equipment, Supplies, Travel,  
Other Expenses

An appropriate description of cost category item.

Payment for performance under this Agreement shall be made by the College to Contractor on a cost-reimbursement basis when billed. Any payments made shall be in accordance with the approved rates referred to above.

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**CHARITABLE LEADERSHIP FOUNDATION**

**CONTRACT WITH**

**ALBANY MEDICAL CENTER FOUNDATION**

**CONTRACT MODIFICATION #1**

CONTRACTOR: Charitable Leadership Foundation

ADDRESS: 747 Pierce Road  
Clifton Park, NY 12065

CONTRACTEE: Albany Medical Center Foundation

ADDRESS: 47 New Scotland Avenue, MC-16  
Albany, NY 12208

CONTRACTEE PI: Paul J. Davis, M.D.

GRANT TITLE: "Rescue of hypoxic kidney and muscle cells with pyrroloquinoline  
quinone (PQQ)"

AMC/CRI COST CTR: 302102

CONTRACT PERIOD: April 1, 2000 through March 31, 2002

MAXIMUM COST: \$37,500

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**CONTRACT MODIFICATION #1****"Rescue of hypoxic kidney and muscle cells with pyrroloquinoline quinone (PQQ)"  
Charitable Leadership Foundation and Albany Medical Center Foundation****Description of Modification:**

A. This contract is modified as follows:

**ARTICLE 2. PERIOD OF PERFORMANCE**

The contract termination date is changed to March 31, 2002. The new contract project dates are April 1, 2000 through March 31, 2002.

**ARTICLE 3. COMPENSATION AND PAYMENT**

New funds in the amount of \$ 27,000 (\$ 27,000 direct, \$ 0 indirect) have been added bringing the subcontract total to \$ 37,500. Albany Medical College will establish a subcontract with Dr. Joel Karliner at the Northern California Institute for Research and Education, (NCIRE) Inc. to complete the study indicated in Appendix A. Appendix B is modified as indicated below:

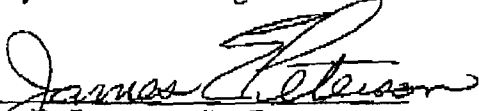
**APPENDIX B. BUDGET TOTALS**

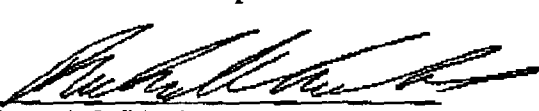
Lab Personnel	\$ 7,000
Supplies	3,500
Subcontract (J. Karliner)	25,000
<u>CRI Administrative Costs</u>	<u>2,000</u>
Direct Cost Total	37,500
<u>Indirect Cost</u>	<u>0</u>
<u>Total Costs</u>	<u>\$37,500</u>

B. Except as modified above, all terms and conditions of this subcontract shall remain unchanged and in full force and effect.

Albany Medical College

Charitable Leadership Foundation

  
James E. Peterson, Ph.D.  
Director of Research Administration

  
Richard C. Liebich  
President

Date: 12/22/00

Date: 1/2/00

**RESEARCH AGREEMENT**  
NO. 223

BY AND BETWEEN

**CHARITABLE LEADERSHIP FOUNDATION  
AND  
ALBANY MEDICAL CENTER FOUNDATION**

This Research Agreement ("Agreement") is entered into and effective as of April 2000, by and between Charitable Leadership Foundation (Tax ID # 16-1514887 (Federal)), a charitable corporation duly organized and existing under the laws of New York and having a principal place of business located at 747 Pierce Road, Clifton Park, NY 12065 ("Sponsor") and the Albany Medical Center Foundation, 47 New Scotland Avenue, MC 57, Albany, NY 12208 ("AMCF").

**RECITALS**

WHEREAS, Sponsor wishes to have certain research services performed in accordance with the scope of work outlined in this Agreement; and

WHEREAS, the performance of such research is consistent, compatible and beneficial to the academic role and mission of AMCF as an institution of higher education; and

WHEREAS, AMCF is qualified to provide such research services.

**AGREEMENT**

NOW, THEREFORE, for and in consideration of the mutual covenants, conditions and undertakings herein set forth, the parties agree as follows:

1. **Scope of Work.** AMCF agrees to perform for Sponsor certain research ("Research") described in the Scope of Work set forth in Appendix A, which is attached hereto and incorporated herein by this reference.

2. **Period of Performance.** The Project period under this Agreement is intended to commence on 4/1/00 and continue until 3/31/01. The Budget Period shall commence on 4/1/00 and continue until 3/31/01 (Initial Term). This Agreement may be extended for additional periods of performance beyond the Initial Term, upon written approval by Sponsor and AMCF.

3. **Compensation and Payment.**

3.1 **Compensation.** Sponsor shall pay to AMCF a TOTAL of the amount \$10,500.00 for performance of the Research under this Agreement, as itemized in Appendix B, attached hereto.

3.2 **Payment.** Sponsor shall pay the Compensation in one payment in advance.

Invoices shall be delivered to:

JENNIFER L. PATTERSON  
CHARITABLE LEADERSHIP  
FOUNDATION  
747 PIERCE ROAD  
CLIFTON PARK, NY 12065

4. **Supervision by Sponsor.** The person with primary responsibility for supervision of the performance of the Research on behalf of Sponsor shall be Richard C. Liebich, or such other person as may be designated by Sponsor, who shall have primary responsibility for technical supervision of the Project.

5. **Reporting Requirements.** AMCF shall provide written reports to Sponsor on the progress of the performance of Research as outlined or required in the Scope of Work. A final written report shall be furnished to Sponsor upon completion of the Research.

6. **Publication.** AMCF agrees that it shall not publish the results of research conducted in connection with this Agreement, without the prior written consent of Sponsor, until the expiration of six (6) months following the first to occur of either the termination of this Agreement or submission of the final written report required under Section 5 hereof. In the event AMCF wishes to publish research results prior to the expiration of the above described six (6) month period, AMCF shall first provide to Sponsor written notice of AMCF's intent to publish and a draft of such publication. Sponsor shall have thirty (30) days after receipt of the draft publication to request in writing the removal of portions deemed by Sponsor to contain confidential or patentable material owned by Sponsor, or to request a delay in submission of the draft for publication pending Sponsor's application for patent protection.

7. **Indemnification.**

7.1 **Indemnification by AMCF.** AMCF shall indemnify, defend and hold harmless Sponsor, its directors, officers, agents and employees against any actions, suits, proceedings, liabilities and damages that may result from the negligent acts or omissions of AMCF, its officers, agents or employees in connection with this Agreement.

7.2 **Indemnification by Sponsor.** Sponsor shall indemnify, defend and hold harmless AMCF, its directors, officers, agents and employees against any actions, suits, proceedings, liabilities and damages that may result from the negligent acts or omissions of Sponsor, its officers, agents or employees in connection with this Agreement. Sponsor shall indemnify the Albany Medical College against any charges of patent infringement brought in any suit by a Third Party and Sponsor shall have the right to choose counsel and control the defense of any such suit, at Sponsor's expense.

8. **Relationship of Parties, Compliance.** In assuming and performing the obligations of this Agreement, AMCF and Sponsor are each acting as independent parties and neither shall be considered or represent itself as a joint venturer, partner, agent or employee of the other. In performance of the Research, Sponsor and AMCF shall comply with all applicable federal, state and local laws, codes, regulations, rules and orders. The Sponsor shall own all rights, title and interest in all inventions and improvements conceived or reduced to practice by AMCF or AMCF personnel in the performance of the Research and may, at its election, file all patent applications relating thereto.

9. **Termination.** This Agreement may be terminated by either party at any time and from time to time, by giving written notice thereof to the other party. Such termination shall be effective thirty (30) days after receipt of such notice. Termination shall not relieve either party of any obligation or liability accrued hereunder prior to such termination, or rescind or give rise to any right to rescind any payments made prior to the time of such termination.

10. **Miscellaneous.**

10.1 **Entire Agreement.** This Agreement, with its attachments, constitutes the entire agreement between the parties regarding the subject matter hereof and supersedes any other written or oral understanding of the parties. This Agreement may not be modified except by written instrument executed by both parties. Neither party shall assign or transfer any interest in this Agreement, nor assign any claims for money due or to become due under this Agreement, without the prior written consent of the other party. This Agreement shall be binding upon and inure to the benefit of the parties, their successors and permitted assigns.

10.2 **Notices.** Except as provided in Section 3 hereof regarding payment of invoices, any notice or other communication required or permitted to be given to either party hereto shall be in writing and shall be deemed to have been properly given and effective: (a) on the date of delivery if delivered in person during recipient's normal business hours; or (b) on the date of delivery if delivered by courier, express mail service or first-class mail, registered or certified, return receipt requested. Such notice shall be sent or delivered to the respective addresses given below, or to such other address as either party shall designate by written notice given to the other party as follows:

In the case of AMCF  
**Technical**

Dr. Paul Davis  
Clinical Research Initiative  
Albany Medical College, MC#16  
47 New Scotland Ave.  
Albany, NY 12208

**Contractual**

James E. Peterson, PhD  
Director Research Administration  
Albany Medical College  
47 New Scotland Ave.  
Albany, NY 12208

In the case of Sponsor:  
**Technical**

Richard C. Liebich  
Position: \_\_\_\_\_  
Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Contractual**

JENNIFER L. PATTERSON  
CHARITABLE LEADERSHIP  
FOUNDATION  
747 PIERCE ROAD  
CLIFTON PARK, NY 12065

10.3 **Governing Law and Disputes.** This Agreement shall be interpreted and construed in accordance with the laws of the State of New York, without application of any principles of choice of laws. Disputes that cannot be resolved by Sponsor and AMCF shall be determined by a court of competent jurisdiction in the State of New York.

IN WITNESS WHEREOF, the parties have caused this Agreement to be executed by their duly authorized representatives effective as of the day and year first written above.

**CHARITABLE LEADERSHIP FOUNDATION  
FOUNDATION**

By:   
Signature

Name: Richard C. Liebich  
Title: President

Date: 7/5/00

**ALBANY MEDICAL CENTER**

By:   
Signature

Name: James E. Peterson, PhD  
Title: Director Research Administration

Date: 8/4/00

Reviewed by:

  
Signature

Name: Paul J Davis, MD  
Title: Principal Investigator

Date: 8/4/00

Appendix A

November 29, 1999

**TITLE OF PROJECT:** Rescue of hypoxic kidney and muscle cells with pyrroloquinoline quinone (PQQ)

**INVESTIGATORS:** Faith B. Davis, Paul J. Davis, Hung-Yun Lin  
Clinical Research Initiative, Albany Medical College-Wadsworth  
Center, New York State Department of Health

**Background.** Reactive oxygen species (ROS) accumulate in mammalian cells during hypoxia/ischemia. While ROS are themselves toxic, it is restoration of normal oxygen tension and blood flow in tissues that is particularly associated with cell necrosis and injury ("reperfusion injury"). Such injury may be mediated by increases in intracellular calcium concentration or local generation of toxic products, such as excitatory amino acids in the case of the central nervous system. A number of substances that scavenge ROS are under study as potential therapeutic agents in managing ischemia. Among these is pyrroloquinoline quinone (PQQ), a naturally-occurring redox compound that also facilitates electron transport in mitochondria. PQQ has been found in preliminary studies to effect neuronal rescue a model of stroke in rats when administered close in point of time to the ischemic insult. However, all organs are subject to ischemic damage and reperfusion injury. In addition to the central nervous system, organs of special concern during hypoxia are the heart, kidney, liver and bowel.

**Hypothesis.** We hypothesize that PQQ in micromolar concentrations will support normal function in hypoxic kidney cells, endothelial cells and heart cells studied *in vitro*. [Endothelial cells line blood vessels and are important sources of chemicals, such as nitric oxide (NO), that maintain normal normal blood supply to organs under conditions of decreased oxygen tension.] In preliminary tests of this hypothesis, we propose to measure certain functions in kidney, endothelial and heart cells maintained under low oxygen tension in the presence and absence of PQQ.

**Experiments Proposed.** Mammalian kidney cells (293T), human endothelial cells (HUVECs) and rat heart-derived muscle cells will be studied. Cells will be maintained in culture under 95% O<sub>2</sub>, 5% CO<sub>2</sub> and in standard media, according to methods we have previously described. We will then expose samples of cells to 50% O<sub>2</sub>, 5% CO<sub>2</sub>, 45% N<sub>2</sub> or 0% O<sub>2</sub>, 5% CO<sub>2</sub>, 95% N<sub>2</sub> for 10-180 minutes; subsequently, the cells will be returned to basal conditions (95% O<sub>2</sub>, 5% CO<sub>2</sub>). Control cells will be those maintained at 95% O<sub>2</sub>, 5% CO<sub>2</sub> in parallel to the experimental samples.

Experimental cells will be sampled under basal conditions and at various time points and results compared with those from control cells sampled serially for the 180-minute study periods.

Measurements to be made are:

- 1) State of mitogen-activated protein kinase (MAPK; ERK1, ERK2) activity (phosphorylation, nuclear translocation), an enzyme that is stimulated by various stresses;
- 2) Response of cells to exposure to specific cytokines or growth factors; the latter include tumor necrosis factor- $\alpha$ , thyroid hormone, epidermal growth factor and, for HUVECs only, vascular endothelial growth factor (VEGF); the responses to be measured are activation of signal transducer and activator of transcription (STAT) proteins (STAT1 $\alpha$ , STAT3, STAT5) and activation of MAPK;
- 3) Cell viability, by the dye exclusion technique;
- 4) Creatine phosphokinase (CPK) release by muscle cells;
- 5) NO generation by HUVECs.

Media pH will be recorded serially through the studies. PQQ (1-100  $\mu$ M) will be added to one of each pair of aliquots of cells.

**Expected results and pitfalls.** It is expected that hypoxia will activate MAPK in all three types of cells and will blunt cellular responses to cytokines and growth factors. Hypoxia will cause CPK release from heart muscle-derived cells and NO release from endothelial cells. PQQ is expected to reduce the effects of hypoxia and to be protective particularly during the phase of return of hypoxia-stressed cells to normal oxygen tension (= phase of reperfusion injury in the intact heart).

All of the assays, except those for CPK and NO, are currently available in our laboratory. CPK will be measured by ELISA and NO will be assayed in the laboratory of Dr. Patricia Phillips (Albany VAMC).. No technical problems are anticipated in carrying out these studies.

**Timetable.** It is estimated that the studies proposed can be completed in 4-6 months.

**Future Directions.** If PQQ is shown to be protective in these three clinically relevant cell lines, then the agent will be tested in the working, isolated-perfused rat heart (Langendorff) model.<sup>1</sup>

## Appendix B

### BUDGET

Faculty salary (0.30 FTE X 6 months)(H-Y Lim)	\$	7500
Culture supplies		2000
Growth factors, cytokines		500
NO, CPK assays		500

TOTAL

\$ 10,500

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'The estimated cost of conducting studies in 40 Langendorff preparations is \$7500-\$10,000 (R. Weischaar, Coromed, Inc., Albany, NY). There are only two commercial laboratories in the U.S. that currently work with the isolated-perfused rat heart: SBI (San Diego) and Chrysallis (Harrisburg area).

PJD/p

**TITLE OF PROJECT:** **Rescue of Ischemic Myocardium with Pyrroloquinoline Quinone (PQQ) in the Isolated Perfused Rat Heart**

**INVESTIGATORS:** Paul J. Davis, M.D.  
Faith B. Davis, M.D.  
George L. Drusano, M.D.  
Albany Medical College

**DATE:** October 22, 1999; revised March 6, 2000

**Background.** Reactive oxygen species (ROS) accumulate in mammalian cells during hypoxia/ischemia. While ROS are themselves toxic, it is the restoration of normal oxygen tension and blood flow in tissues that is particularly associated with cell necrosis and injury ("reperfusion injury"). Such ROS-caused injury may be mediated by increases in intracellular calcium concentration or by local generation of toxic products, such as N-methyl-D-aspartate (NMDA) in the case of ischemia of the central nervous system. A number of substances that scavenge ROS are under study as potential therapeutic agents in the management of ischemia in several organs. Pyrroloquinone quinone (PQQ) is a naturally-occurring redox compound with several biological properties (1,2). These properties include the scavenging of free radicals. The compound has been tested in a rat model of cerebral hemisphere ischemia and has been shown to be effective in neuronal rescue (3). An additional mechanism of action of PQQ in this model is to diminish the ROS response to glutamate through an action at the NMDA receptor redox site (4). PQQ has been administered in the isolated rabbit heart preparation and served to reduce total lactic dehydrogenase (LDH) release in the setting of reperfusion (5). Cardiac performance was not monitored.

**Hypothesis.** We hypothesize that PQQ will support normal function in hypoxic/ischemic heart cells.

**Proposal.** We propose to test the ability of PQQ to salvage ischemic myocytes in the setting of globally hypoxic myocardium in the working isolated perfused rat heart model. PQQ at micromolar concentrations (1-50  $\mu$ M) will be administered via perfusate in this model. The endpoints are recovery of work capacity, restoration of heart rate and limitation of release from heart cells into effluent of myocardial proteins that signal ischemia, e.g., LDH, troponin T, myoglobin and creatine phosphokinase (area under the curve, AUC, of the proteins post-ischemia and treatment). Results will be compared with those from hearts that did not receive PQQ.

**Additional applications of PQQ relevant to ROS.** It is also proposed that PQQ will protect against post-perfusion damage in the ischemic/hypoxic liver, kidney, gastrointestinal tract and noncardiac muscle. We also suggest that the agent will be of value in the preservation of organ function in patients with profound, spontaneous hypothermia who are subjected to active re-warming. Finally, we propose that PQQ may be useful in the preservation of function in organs temporarily maintained *ex vivo* for subsequent transplantation.

### References

1. Gallop PM, MA Paz, R Fluckiger, HM Kagan. 1989. PQQ, the elusive coenzyme. TIBS 14:343-346
2. Paz MA, R Fluckiger, PM Gallop. 1992. The Biomedical Significance of PQQ. In Davison VL (ed.), Principles and Applications of Quinoproteins. New York: Marcel Dekker, Inc., ch 17, pp 381-393
3. Jensen FE, CJ Gardner, AP Williams, PM Gallop, E Aizenman, PA Rosenberg. 1994. The putative essential nutrient pyrroloquinolone quinone is neuroprotective in a rodent model of hypoxic/ischemic brain damage. Neuroscience 62:399-406
4. Scanlon JM, E Aizenman, IJ Reynolds. 1997. Effects of pyrroloquinoline quinone on glutamate-induced production of reactive oxygen species in neurons. Eur J Pharmacol 326:67-74
5. Xu F, CP Mack, KS Quandt, M Schlafer, V Masey, DE Hultquist. 1993. Pyrroloquinoline quinone acts with flavin reductase to reduce ferryl myoglobin *in vitro* and protects isolated heart from re-oxygenation injury. Biochem Biophys Res Comm 193:434-439

**Title: USE OF PYRROLOQUINOLINE QUINONE TO RESCUE ISCHEMIC CELLS**

**Abstract.** Pyrroloquinoline quinone (PQQ) is a naturally-occurring redox compound with several biologic properties. These properties include the scavenging of reactive oxygen species (ROS; free radicals). The compound has been tested in a rat model of cerebral hemisphere ischemia and has been shown to be effective in neuronal rescue. PQQ has also been administered in the isolated rabbit heart preparation and served to reduce total lactic dehydrogenase (LDH) release in the setting of reperfusion. Cardiac performance was not monitored. We propose that PQQ in micromolar concentrations in the globally hypoxic heart restores work capacity and heart rate and limits release of myocardial proteins that signal ischemic damage. It is also proposed that PQQ will rescue reperfusion damage in the ischemic/hypoxic liver, kidney, gastrointestinal tract and noncardiac muscle. PQQ will be of value in the preservation of organ function in patients with profound, spontaneous hypothermia who are subjected to active re-warming. It is also proposed that PQQ is useful in the preservation of function in organs temporarily maintained *ex vivo* for subsequent transplantation.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**APPLICANT(S):** Davis  
**APPLICATION NO:** 10/146,566 **EXAMINER:** Not yet assigned  
**FILING DATE:** May 15, 2002 **ART UNIT:** 1645  
**FOR:** PYRROLOQUINOLONE QUINONE DRUGS FOR THE TREATMENT OF CARDIAC  
INJURY AND METHODS OF USE THEREOF

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P.O. Box 1450  
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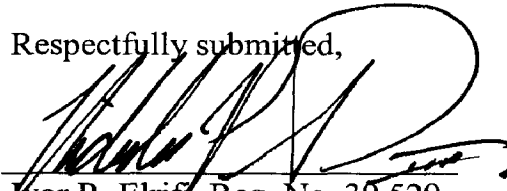
**TRANSMITTAL LETTER**

Transmitted herewith for filing in the above-referenced application are the following documents:

1. Assignment Recordation Cover sheet (1 p.);
2. Research Agreement (24 pp.);
3. Check No. 17105 for \$40.00; and
4. Return Postcard.

If the enclosed papers are considered incomplete, the Mail Room is respectfully requested to contact the undersigned collect at the number provided below. The Commissioner is authorized to credit any overpayment or charge any deficiencies to Deposit Account No.50-0311, Reference No. 19705-029. A duplicate copy of this transmittal letter is enclosed.

Respectfully submitted,



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Dated: September 11, 2003

Please address all correspondence to Customer No.: 30623.

Express Mail Label No.: EV 328186878 US  
Date of Deposit: September 11, 2003

Attorney Docket No. 19705-029

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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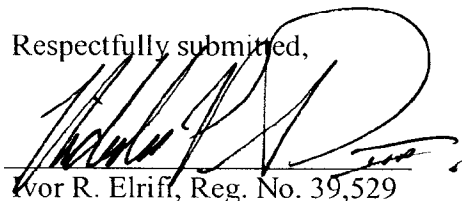
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TRA 1831156v1

**RECORDED: 09/11/2003**

**PATENT**  
**REEL: 014483 FRAME: 0842**