08:09:33 OCA PAD AMENDMENT - PROJECT HEADER INFORMATION 07/12/91

Active

Project #: E-25-M10 Cost share #: Rev #: 2
Center # : 10/24-6-R6966-1A0 Center shr #: OCA file #:
Work type : RES
Contract#: LETTER DTD 5/14/91 Mod #: ADMIN 7/12/91 Document : CONT
Prime #: 5 R01 HL41175-04 Contract entity: GTRC

Subprojects ? : N CFDA: N/A
Main project #: PE #: N/A

Project unit: MECH ENGR Unit code: 02.010.126
Project director(s):
NEREM R M MECH ENGR (404)894-2768

Sponsor/division names: UNIVERSITY OF TEXAS / SAN ANTONIO, TX
Sponsor/division codes: 400 / 045

Award period: 910501 to 920430 (performance) 920730 (reports)

Sponsor amount	New this change	Total to date
Contract value	0.00	86,347.00
Funded	0.00	86,347.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: VASCULAR HEALING - CELL BIOLOGY & RHEOLOGIC FACTORS

PROJECT ADMINISTRATION DATA

OCA contact: Kathleen R. Ehlinger 894-4820

Sponsor technical contact

COLIN J. SCHWARTZ
(512)567-4035

UNIVERSITY OF TEXAS
7703 FLOYD CURL DRIVE
SAN ANTONIO, TEXAS 78284-7862

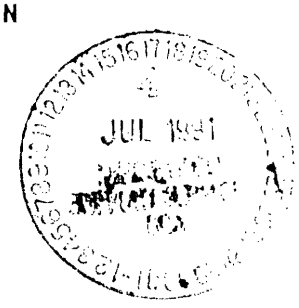
Sponsor issuing office

R.B. PRICE
(512)567-2000

UNIVERSITY OF TEXAS
7703 FLOYD CURL DRIVE
SAN ANTONIO, TX 78284-7862

Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : N/A NIH supplemental sheet
Equipment title vests with: Sponsor GIT X

Administrative comments -
ISSUED TO CORRECT BUDGET TO REFLECT ORIGINAL AWARD.



GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 05/21/92

Project No. E-25-M10 Center No. 10/24-6-R6966-1A0

Project Director NEREM R M School/Lab MECH ENGR

Sponsor UNIVERSITY OF TEXAS/SAN ANTONIO, TX

Contract/Grant No. LETTER DTD 5/14/91 Contract Entity GTRC

Prime Contract No. 5 R01 HL41175-04

Title VASCULAR HEALING - CELL BIOLOGY & RHEOLOGIC FACTORS

Effective Completion Date 920430 (Performance) 920730 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	Y	
Final Report of Inventions and/or Subcontracts	Y	
Government Property Inventory & Related Certificate	N	
Classified Material Certificate	N	
Release and Assignment	N	
Other	N	

Comments

Subproject Under Main Project No.

Continues Project No. E-25-M44

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
Other	N
	N

NOTE: Final Patent Questionnaire sent to PDPI.

E25-M10

Georgia Tech

Georgia Institute of Technology
Atlanta, Georgia 30332-0405

Robert M. Nerem, Ph.D.
Institute Professor and
Parker H. Petit Chair
for Engineering in Medicine
School of Mechanical Engineering
(404) 894-2768

May 12, 1992

TO: Pete Dawkins

FROM: Bob Nerem

SUBJECT: Continuation Proposal including Progress Report for E25-M10

Attached is the continuation proposal for the project entitled "Vascular Healing: Cell Biology and Rheologic Factors." Contained within it is the progress report for the fourth year of this project, including the work done on E25-M10 here at Georgia Tech. It also includes the proposal for the Georgia Tech part of the fifth and final year.

RMN:cmw
Encl.

The University of Texas
Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, Texas 78284-7750

Department of Pathology

(512) 567-4000

(512) 567-4035
Fax: 567-3105

March 4, 1992

National Institutes of Health
NHLBI-DEA
Grants Operations Branch
Westwood Building, Room 4A09A
Bethesda, Maryland 20816

RE: Grant No. 5R01HL41175-05

Dear Sir or Madam:

Please find enclosed the completed application for continuation grant, "Vascular Healing - Cell Biology and Rheologic Factors". We apologize for the delay and would appreciate your acceptance of this continuation grant.

Sincerely,

Colin J. Schwartz, M.D., FRACP
Professor
Department of Pathology

The University of Texas
Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, Texas 78284-7828

Office of the Director of
Grants Management

(512) 567-2340

March 4, 1992

National Institutes of Health,
NHLBI-DEA
Grants Operations Branch
Westwood Building, Room 4A09A
Bethesda, Maryland 20816

Dear Sir or Madam:

We are enclosing a letter and three (3) copies of an application for continuation of grant number HL41175-05 for research entitled "Vascular Healing--Cell Biology and Rheologic Factors" directed by Dr. Colin J. Schwartz, Professor of Pathology.

This continuation application qualifies under the Federal Demonstration Project's pilot project relating to the non-competing application process. As such, the application consists of a cover page and technical progress report.

Funding is requested at the recommended level for the period May 1, 1992 through April 30, 1993.

We shall appreciate your favorable consideration of this proposal and will be pleased to furnish any additional information which may be required.

Sincerely yours,

E.A. Siebold
Director
Grants Management

EAS/KJN:kyp

Enclosures: 4

xc: Dr. Colin J. Schwartz

SECTION I

320

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

APPLICATION FOR CONTINUATION GRANT

OMB No 0925-0001

REVIEW GROUP	TYPE	ACTIVITY	GRANT NUMBER *(Insert on all pages)*
SRC (18)	5	R01	HL41175-05

TOTAL PROJECT PERIOD
From: 07/01/88 Through: 04/30/93

REQUESTED BUDGET PERIOD
From: 05/01/92 Through: 04/30/93

To be verified by applicant. Check information in items 1 through 6. If incorrect, furnish correct information in item 13.

1. TITLE OF PROJECT
VASCULAR HEALING--CELL BIOLOGY AND RHEOLOGIC FACTORS

2a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(name and address, street, city, state, zip code)*
SCHWARTZ, COLIN J
UNIVERSITY OF TEXAS
7703 FLOYD CURL DRIVE
SAN ANTONIO, TEX 78284

4. APPLICANT ORGANIZATION *(name and address, street, city, state, zip code)*
UNIV OF TEXAS HLTH SCI CTR
7703 FLOYD CURL DR
SAN ANTONIO, TX 78284

5. ENTITY IDENTIFICATION NUMBER
17415860318 3

2b. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
PATHOLOGY

2c. MAJOR SUBDIVISION
GRAD SCHOOL OF BIOMEDICAL SCIS

3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR BIOMEDICAL RESEARCH SUPPORT GRANT *(see Instructions)*
20 OTHER

6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION
EXEC VICE PRESIDENT
FOR ADMIN AND BUSINESS AFFAIRS
UNIV OF TEXAS HLTH SCIE CTR
7703 FLOYD CURL DR
SAN ANTONIO, TX 78284

Complete the following *(see Instructions)*

7. HUMAN SUBJECTS
7a. ☐ NO ☒ YES { ☐ Exemption # _____ OR ☒ IRB Approval Date 7/9/91
7b. Assurance of Compliance # M-1403

8. VERTEBRATE ANIMALS
8a. ☐ NO ☒ YES ... IACUC Approval Date 5/15/91
8b. Animal Welfare Assurance # A3345-01

9. PERFORMANCE SITE(S) *(organizations and addresses)*
1. The University of Texas Health Sci Ctr
Department of Pathology
7703 Floyd Curl Drive
San Antonio, Tx. 78284-7750

2. The George W. Woodruff SChool of
Mechanical Engineering
Georgia Institute of Technology
S.S.T. BG, Ferst Street
Atlanta, GA 30322-0405

10. COSTS REQUESTED FOR BUDGET PERIOD
10a. DIRECT $ 171,351 | 10b. TOTAL $ 207,271

11. INVENTIONS *(see Instructions)*
☒ NO ☐ YES { ☐ Previously reported OR ☐ Not previously reported

TELEPHONE INFORMATION

	AREA CODE	TELEPHONE NO. AND EXTENSION
12a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Item 2a)* Colin J. Schwartz, M.D.	512	567-4035
12b. NAME OF BUSINESS OFFICIAL *(Item 6)* Robert B. Price	512	567-2000
12c. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Item 15)* E. A. Siebold Director Grant Mgmt.	512	567-2340

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWERS APPLY.

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense. *(U.S. Code, Title 18, Section 1001.)*	SIGNATURE OF PERSON NAMED IN 2a *(In Ink. "Per" signature not acceptable)* Colin J. Schwartz, M.D.	DATE 3/3/92
15. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense. *(U.S. Code, Title 18, Section 1001.)*	SIGNATURE OF PERSON NAMED IN 12c *(In Ink. "Per" signature not acceptable)* E.A. Siebold	DATE

RETURN COMPLETED APPLICATION TO PHS AS SOON AS POSSIBLE:
NO LATER THAN 1 MARCH 1992

Schwartz, Colin J.
283-70-9432

1. Brief Summary of Plans:

Based on encouraging and continuing progress this year (-04), no major changes in our overall research plan are anticipated. The primary plan for the -05 year is to achieve the final steps of the ultimate goal of both the RFA and our original proposal, i.e., to develop and test a successful small diameter vascular graft. Also, a major emphasis will be placed upon submitting several manuscripts emanating from our studies for publication. The changes to our original research plan, which are detailed below, reflect recent rapid developments in our knowledge concerning cytokines and cell adhesion molecules influencing endothelial cell-to-cell, cell-to-substrate, as well as platelet and monocyte adherence to endothelial cells. Also, progress with the *in vitro* testing of the polyester mesh graft this year has allowed us to refine the endothelial seeding, incubation, and shear stress preconditioning of the graft and, thus, improve the feasibility for *in vivo* implantation. Additionally, progress in our laboratories at UTHSCSA and GIT, especially related to shear stress influences on endothelial cell-to-substrate focal adhesion points and endothelial secretory product(s) influencing monocyte recruitment and adhesion, have allowed us to focus more precisely our efforts to optimize both development of a pre-endothelialized vascular graft and also probe cellular mechanisms regulating the biology of vascular endothelial cells residing in different flow environments.

Initial objectives established for Specific Aim #1 directed at defining endothelial cell growth on porous graft materials under steady or pulsatile flow conditions have been achieved. Some studies will continue to explore molecular mechanisms governing the shear dependent decrease in cell proliferation observed. The knowledge gained from these studies has allowed us to initiate *in vitro* testing of a confluent pre-endothelialized vascular graft. Additionally this year, we plan to continue a collaboration initiated in the current year with Dr. Dan Urry at The University of Alabama at Birmingham to examine the influence of elevated laminar shear stress on the proliferation and retention of BAEC cultured on synthetic elastomeric polypeptides.

Since most of the major objectives of Specific Aim #2 designed to determine influence of different shear stress environments on graft endothelial monolayer integrity have been completed, plans for this year will focus on cellular and molecular mechanisms regulating the expression and distribution of cell-to-substrate focal adhesion sites. At UTHSCSA, the primary objective within this Aim will be to perform immunocytochemistry studies on the expression of the junctional protein, ENDOCAM, as modified by shear stress exposure. This effort will complete current studies demonstrating a shear-related change in cellular ENDOCAM mRNA. Based on current results detailed below demonstrating that BAEC exposed to prolonged high shear stress exhibited a dramatic change in distribution of key extracellular matrix components including fibronectin, collagen, and laminin, the focus this year at GIT will be to expand these studies to pulsatile flow regimens designed to more closely model *in vivo* flow patterns.

The objectives of Specific Aim #3 to examine the influence of shear stress preconditioning of BAEC on platelet and monocyte adherence have been achieved. Efforts within Aim #3 will be directed at completing studies on the influence of the shear stress environment on BAEC expression of mRNA levels for the monocyte chemoattractant, MCP-1, and the endothelial adhesion molecule, VCAM-1, which mediates monocyte-endothelium interaction. Plans in Specific Aim #4 to develop and test a preconditioned, endothelialized vascular prosthesis both *in vitro* and *in vivo* have been initiated and are designed to be completed within year -05. As is evident in the progress in year -04, continued success in this program involves and depends upon an integrated and coordinated effort among the investigators at both UTHSCSA and GIT.

2. Current Studies:

Specific Aim #1: Since the primary objectives of this aim were completed in the first two years, and are currently providing the basic endothelialized material for the other 3 specific aims, studies have been expanded to examine some of the molecular mechanisms mediating the pronounced decrease in BAEC and PAEC proliferation observed in response to elevated shear stress. Specifically, studies performed in a collaborative effort between the laboratories of Dr. R. M. Nerem of GIT and Dr. B.C. Burk at Emory University indicate that BAEC cultures preconditioned for 24 h to elevated steady state laminar or pulsatile shear stress exhibited a decreased percentage of cells in the S phase of the cell cycle accompanied by an increase in the percentage of cells in the G_0/G_1 phase as compared to no flow control cells using flow cytometry. Secondly, this same collaborative group (Mitsumata et. al.) demonstrated that BAEC preconditioned to elevated shear stress exhibited a seven-fold decreased response in cellular mRNA levels for c-myc protein relative to control BAEC when the cells were challenged with a pharmacological dose of α-thrombin. Finally, Mitsumata et.al. demonstrated that prolonged elevated shear stress exposure was associated with an increase in c-cis mRNA levels concomitant with a decrease in glyceraldehyde 3-phosphate dehydrogenase intracellular mRNA levels. These observations suggest that these cells do not break their cell-to-substrate attachments upon division and, thus, may have important implications relative to the maintenance of vascular endothelial integrity in high flow and shear stress environments.

Specific Aim #2: As mentioned above, studies at UTHSCSA within this aim have been directed at observing shear stress related responses of an important cell-to cell adhesion molecule, ENDOCAM (CD31). In the original proposal, we hypothesized that preconditioning cultured EC to elevated shear stress, would enhance integrity of the endothelial monolayer via increasein molecules, such as ENDOCAM involved in EC-EC junctions. During this year, we have completed studies demonstrating a significant increase in intracellular ENDOCAM mRNA levels in cells preconditioned to elevated shear stress. This increased ENDOCAM mRNA level can be detected as early as 3h after shear initiation and becomes pronounced by 24h. These levels remained elevated up to 96h in high shear stress exposed cells relative to low shear stress (< 1 dyne/cm^2) treated cells. Interestingly, mRNA levels for molecules such as MCP-1 appear to be changing in the opposite direction in response to the shear stress regimens. Current studies are directed at using an ENDOCAM antibody generously provided by Dr. Steve Albelda to determine whether the mRNA changes are paralleled by actual changes in ENDOCAM protein expression at cell-to-cell junctions.

Immunofluorescent studies (Drs.. Girard and Nerem, GIT) The fibronectin, laminin, collagen type IV and vitronectin present in BAEC and their associated ECM were observed by immunofluorescence. In static cultures, fibronectin formed a dense fibrillar network, randomly oriented. In order to determine where fibronectin was present, the cell layer was removed with either deoxycholic acid or EGTA treatments. Most of the fibrillar fibronectin appeared to remain on the culture dish. It was deduced that the fibrillar fibronectin observed belonged mostly to the EC deposited by endothelial cells at their basal side. When BAEC were exposed to a shear stress of 70 dyn/cm^2 for 24 hours, the cells elongated and aligned with the direction of flow, as previously reported, and the fibronectin fibrils showed a preferential alignment with the direction of flow.

In static cultures, laminin and collagen type IV both showed a diffuse fibrillar pattern, randomly oriented, as well as a spotty staining, thought to be intracellular. As for fibronectin, removal of the cellular layer revealed that lamin and collagen type IV were mostly deposited in

the basal ECM. When BAEC were submitted to a shear stress of 70 dyn/cm^2 for 24 hours, both laminin and collagen type IV reorganized into a network of thick fibers, randomly oriented.

Vitronectin did not appear as a matrix, but its staining seemed to coincide with the pattern of endothelial cells, suggestive of intracellular staining. When the cell layer was removed by treatments with either deoxycholic acid or EGTA, the material remaining on the culture dish showed no staining for vitronectin. Hence vitronectin appeared to be essentially intracellular. When the cells were exposed to a 70 dyn/cm^2 shear stress for 24 hours, no major change in the vitronectin staining was observed.

Immunoblotting studies (Drs. Girard and Nerem, GIT) The quantities of fibronectin, laminin and vitronectin in endothelial cells and their ECM were determined by immunoblotting and scanning laser densitometry. Fibronectin appeared as a doublet of two subunits of 220 kDa each. Laminin had three subunits: a doublet migrating at 210 kDa and a third subunit larger than 300 kDa which did not enter the separating gels. Vitronectin migrated as two subunits: one major band migrated at 70 kDa and one minor band at 50 kDa. The ratio R (a measure of the relative quantity of fibronectin, laminin or vitronectin in sheared cells versus control cells expressed in percentage was obtained for a shear stress of 50 dyn/cm^2 at three different time points: 12, 24 and 48 hours (figure 9). For all three proteins studied, the values of the parameter R at 12, 24 and 48 hours time points were not found to be significantly different (when compared by analysis of variance). This suggests that fibronectin, laminin and vitronectin levels in BAEC did not vary over time in response to a 50 dyn/cm^2 shear stress.

The morphological reorganization of fibronectin in BAEC exposed to shear stress has already been reported. The additional rearrangement of laminin and collagen type IV into thick fibers further show that endothelial cells modify their ECM in response to flow. The mechanism by which this modification occurs is unknown: does the cytoskeleton, in its process of elongation, provide signals to the ECM through transmembrane linkages such as focal contacts? Or is the ECM itself triggered by another pathway, which communicates with the actin and myosin filaments involved in the generation of cell elongation and orientation?

The fact that the amounts of laminin and vitronectin did not change over time supports the hypothesis that BAEC do not change the equilibrium synthesis/degradation of their ECM components in response to flow. A change in the organization of the ECM such as that reported above might be sufficient for endothelial cells to modify their adherence and change their shape when exposed to shear stress. Levels of $\alpha_5\beta_1$ FNRs in BAEC that have been exposed to a steady laminar shear stress of 30 dynes/cm were determined using an immunoblot analysis. U under reducing conditions, the α_5 and β_1 subunits migrated on SDS-polyacrylamide gels at 150- and 140-kDa, respectively. Following 6 hr. of exposure to shear stress, the levels of the α_5 subunit showed an approximately 30% increase in levels compared to the amount present in cells growing under static culture conditions. There was a further increase at 24 and 48 hr. with cells subjected to flow showing a nearly two-fold increase in the levels of the α_5 subunit compared to static cultures. There appeared to be no change in the levels of the β_1 subunit.

An examination of the $\alpha_v\beta_3$ VNRs immunoblotting analysis showed the presence of an α_v subunit migrating at 125 kDa and a β_3 subunit migrating at 105 kDa. Flowing 6 hr of exposure to flow, there appeared to be no change in the levels of either subunit. However, at both 24 and 48 hr, there appeared to be a three-fold increase in the level of the β_3 subunit. Levels of the α_v subunit appeared not to change in response to flow.

In order to examine receptors for collagen and laminin, levels and localization of the integrin subunits α_2 and α_3 were examined. These subunits did not appear to localize in focal adhesions. In static cultures of BAECs, the α_3 subunit appeared to be evenly distributed throughout the cells. Cells subjected to shear stress for 24 hr showed little evidence of a change in localization or levels of α_3. The α_2 subunit was concentrated in a perinuclear location in cells in static culture, perhaps relecting synthesis of the subunit. Following 24 hr of exposure to shear stress, there was a dramatic increase in the perinuclear staining for α_2 compared to static controls. These studies indicate that integrins are differentially regulated in ECs exposed to a flow environment.

Specific Aim #3: Understanding platelet-endothelial and monocyte endothelial interactions is critical not only to development of a small diameter vascular graft which can maintain patency *in vivo* but also to investigate the basic cellular processes mediating thrombosis and atherogenesis. Studies in year -04 within Specific Aim #3 have been concentrated on determining the cellular mechanisms regulating the previously documented decreased platelet and monocyte adherence to BAEC preconditioned for 24 h elevated shear stress. Previous studies by Dr. Cayatte at UTHSCSA have demonstrated that the decrease in platelet and monocyte adherence observed in cells preconditioned to elevated shear stress (30 dynes/cm^2) relative to BAEC preconditioned to low shear stress (< 1 dyne/cm^2) is a time dependent process requiring a minimum of 4 h for expression. The results of these studies have recently been submitted for publication. Based on the results of these studies, the efforts of the current year (04) have been focused upon measuring cellular mRNA levels for the monocyte chemotactic protein, MCP-1, and vascular cell adhesion molecule, VCAM in EC preconditioned to both low (< dyne/cm^2) and high (30 dynes/cm^2) shear stress levels. Since the level of these two messenger RNA molecules is very low in static cultured cells, experiments were designed to examine the influence of shear stress preconditioning of EC on their subsequent ability to express increased MCP-1 and VCAM-1 mRNA levels in response to a lipopolysaccharide (LPS) stimulus previously reported to elicit a maximal response of these two genes. The results of these studies indicate that while static cultured BAEC exhibited a typical high level of MCP-1 and VCAM-1 mRNA expression in response to LPS, EC preconditioned to elevated shear stress exhibited little or no response to LPS. These results were paralleled in monocyte adherence studies. Thus, high shear preconditioned, LPS-treated cells exhibited an adherence level similar to that observed for untreated control cells, while no shear, LPS-treated cells exhibited a more than 10-fold increase in monocyte adherence relative to static untreated BAEC. To determine the time course required for this shear related inhibition, these studies were repeated using shear stress preconditioning times ranging from 30 minutes to 4 h prior to the 5 h LPS treatment exposure. The results of these studies indicate that a minimum of 1 h of elevated shear stress is required to observe a detectable inhibition in the response of MCP-1 or VCAM mRNA expression to LPS with the maximum response requiring a 4 h high shear stress exposure. Thus, these findings indicate that preconditioning BAEC to elevated shear stress is associated with a time dependent loss of sensitivity or even refractoriness to LPS-induced activation as measured by both MCP-1 and VCAM gene expression and monocyte adherence.

Specific Aim #4: Studies were continued within this Aim in the current year to develop and test *in vitro* a small diameter, pre-endothelialized, and shear stress pre-conditioned vascular prosthesis. In cooperation with Spectrum Medical Industries, a 5 mm internal diameter cylindrical tube constructed from the 1 μ porous polyester mesh used in our previous studies has been developed. During this year, several modifications to the *in vitro* flow system had to be made to permit proper defining of flow and shear stress parameters entering and throughout the vascular prosthesis. Current studies are directed toward completing the flow studies *in vitro*

using this pre-endothelialized prosthesis and evaluating cell retention after prolonged pulsatile shear stress conditions as described in our initial design.

3. **Human Subjects:** No change

4. **Vertebrate Animals:** No change

The University of Texas Health Science Center at San Antonio

Certification of Proposals for Research and Other Sponsored Activities

Project Title: Cellular Mechanisms in Atherogenesis
Project Status: New ☐ Continuation ☒ Renewal ☐
Brief Description of Activity:

Studies involve the regulation of endocytosis, the influence of hemodynamic shear stress on endothelial cells, monocyte pathobiology in atherogenesis, and lipoprotein-cellular interactions. The program is supported by biochemistry, electron microscopy and cell culture laboratories.

Principal Investigator(s):

	NAME	ACADEMIC TITLE	DEPARTMENT
(1)	Colin J. Schwartz, M.D.	Professor	Pathology
(2)			

Name of Granting Agency: National Heart Lung and Blood Institute (NHLBI)

This Budget Period: $ 819,578 From 7/01/92 To 06/30/93

Total Project Period:* $ From To

*Does not apply to Continuation.

PART I

INVESTIGATOR AND CHAIRMAN'S CERTIFICATION

The proposed activity:

a. Supports the teaching and research objectives of the department, and can be accommodated within existing space assigned.
b. Salaries conform to those paid from regular University funds.
c. Does not extend the University into the community or state in the role of an advocate or social or political action agency.
d. Does not require long range financial commitments by the University, and does not require new tenure commitments.
e. Involves clinical investigation using human subjects or specimens:
   No ☐ Yes ☒ If yes: Date approved by Institutional Review Board 8/13/91
f. Involves the utilization of animals:
   No ☐ Yes ☒ If yes: Provide Laboratory Animal Resources Committee Protocol No. 89134-99-04-U
g. Use of replicating agents or recombinant DNA experiments:
   No ☐ Yes ☒ If yes: Date approved by Inst. Biohazards Committee
h. Involves use of chemical carcinogens:
   No ☒ Yes ☐ If yes: Date approved by Inst. Chem. Safety Committee
i. Use of Computing Resources:
   No ☒ Yes ☐ If yes: Date approved by Computing Resources
j. Will take place off-campus (including BCH and VA):
   No ☐ Yes ☒ If yes: Date approved by Off-Campus Administration

Exceptions, Comments, Remarks:

Sub-contracts to Georgia Institute of Technology, Atlanta, Georgia

PRINCIPAL INVESTIGATOR	DATE	DEPARTMENT CHAIRMAN	DATE
Colin J. Schwartz, M.D.	4/28/92	David S. Papermaster, M.D.	4/28/92

PART II

ADMINISTRATIVE APPROVAL AND CERTIFICATION

The proposed activity:

a. Conforms to the Rules and Regulations of the Board of Regents.
b. Supports the teaching and research objectives of the school.
c. Excessive cost sharing is not required.
d. All exceptions noted in above are satisfactory.

REMARKS:

Approved:	Approved:	Certified:
Dean — Date	For Executive Vice President for Administration and Business Affairs — Date	For President — Date