17:07:00 OCA PAD INITIATION - PROJECT HEADER INFORMATION 10/04/88

Active

Project #: E-25-614 Cost share #: Rev #: 0
Center # : R6595-0A0 Center shr #: OCA file #:
Work type : RES
Contract#: LTR DTD 880725 Mod #: Document : OTH
Prime #: 1 R01 HL41175 Contract entity: GTRC

Subprojects ? : N
Main project #:

Project unit: ME Unit code: 02.010.126
Project director(s):
NEREM R M ME

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

Award period: 880701 to 890430 (performance) 890430 (reports)

Sponsor amount	New this change	Total to date
Contract value	74,620.00	74,620.00
Funded	74,620.00	74,620.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: VASCULAR HEALING: CELL BIOLOGY AND RHEOLOGIC FACTORS

PROJECT ADMINISTRATION DATA

OCA contact: Ina R. Lashley 894-4820

Sponsor technical contact

DR COLIN SCHWARTZ
(512)567-4035
UNIV OF TEXAS DEPT OF PATHOLOGY
7703 FLOYD CURL DR
SAN ANTONIO TX 78284-7862

Sponsor issuing office

MR EARL SIEBOLD
(512)567-2336
UNIV OF TEXAS HLTH SCI CTR
7703 FLOYD CURL DR
SAN ANTONIO TX 78284-7862

Security class (U,C,S,TS) : U
Defense priority rating : N/A
Equipment title vests with: Sponsor GIT
NONE PROPOSED.

ONR resident rep. is ACO (Y/N): N
N/A supplemental sheet

Administrative comments -
CONSORTIUM AGREEMENT ESTABLISHED UNDER AN NIH GRANT. NIH GRANT GUIDELINES GOVERNS ITS ADMINISTRATION.

12/88

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Date 7/3/89

oject No. E-25-614 Center No. R6595-0A0

oject Director R. M. Nerem School/Lab ME

onsor University of Texas Health Science Center

ntract/Grant No. Agreement dtd 7/27/88 GTRC XX GIT ____

ime Contract No. 1 R01 HL41175

tle Vascular Healing: Cell Biology and Rheologic Factors

fective Completion Date 4/30/89 (Performance) 4/30/89 (Reports)

oseout Actions Required:

__ None
__ Final Invoice or Copy of Last Invoice- Submitted
__ Final Report of Inventions and/or Subcontracts- Patent questionnaire sent to PI.
__ Government Property Inventory & Related Certificate
__ Classified Material Certificate
__ Release and Assignment
__ Other ____

cludes Subproject No(s). ____

oproject Under Main Project No. ____

ntinues Project No. ____ Continued by Project No. E-25-M80

tribution:

__ Project Director
__ Administrative Network
__ Accounting
__ Procurement/GTRI Supply Services
__ Research Property Management
__ Research Security Services
X Reports Coordinator (OCA)
X GTRC
X Project File
Z Contract Support Division (OCA)
__ Other ____

SECTION IV
PROGRESS REPORT SUMMARY

GRANT NUMBER SRC (18)
1 RO1 H141175-02

PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR	PERIOD COVERED BY THIS REPORT	
Schwartz, Colin J.	FROM	THROUGH
APPLICANT ORGANIZATION The University of Texas Health Science Center	4/1/89	3/31/90

TITLE OF PROJECT *(Repeat title shown in item 1 on first page)*
Vascular Healing -- Cell Biology and Rheologic Factors

(SEE INSTRUCTIONS)

1. Brief Summary of Plans:

Based on preliminary data obtained in growth studies, no significant changes in our research plan are anticipated. Specific Aim #1 will be completed within the first 6 months of this next year (-02) and the experiments within Specific Aim 2; to determine the influence of hemodynamic preconditioning on maintenance of endothelial integrity in response to shear stress; and Specific Aim 3; to examine platelet and monocyte adherence on hemodynamically pre-conditioned endothelial cells; will be initiated in year -02 both at UTHSCSA and GIT as outlined in the original proposal.

2. Current Studies:

The initial seven months of this study have concentrated on characterization of the growth of bovine aortic endothelial cells (BAEC) and porcine aortic endothelial cells (PAEC) on several of the proposed substrates. These substrates include 1 micron pore polyester mesh, 1 micron pore dacron, a nonporous polyester film, and nonporous polystyrene (culture ware plastic). Additionally, endothelial cell replication on these surfaces was examined using either the native surface or subsequent to collagen and/or fibronectin coating.

Endothelial cells were seeded at a density of 10^4 cell/cm^2 on the respective substrates. Cell replication was monitored on days 1,3,5,7 after seeding by cell counting, ^{3}H-thymidine incorporation, and ^{3}H-thymidine autoradiography.

The results indicate that endothelial cells seeded upon noncoated polyester mesh, dacron mesh, or nonporous polyester exhibit a slower growth rate and attain a lower maximum number and density relative to cells plated on standard polystyrene culture ware. Either collagen and/or

fibronectin coating of these surfaces allowed endothelial cells to achieve full confluence by day 5 at a number and density similar to that observed on standard culture surfaces. In experiments utilizing coated surfaces, ^{3}H-thymidine incorporation and autoradiograpic labeling were maximum at days 1 and 3 and sharply decreased to a minimum plateau at days 5 and 7.

Current efforts involve examining endothelial cell growth on uncoated vs collagen and/or fibronectin coated mesh under either steady state or pulsatile shear stress conditions. Secondly, current studies are now extending to evaluate PAEC and BAEC growth on expanded polytetrafluoroethylene (ePTFE). This studies were delayed due to difficulty in obtaining the desired material from the original proposed source (W.C. Gore and Associates). We now have ePTFE provided to us by Shiley, Inc., Irvine, CA.

The most significant achievements of the current year involve characterization of endothelial cell growth on several potential vascular graft materials and the attainment of a confluent endothelial cell monolayer on the porous polyester mesh within 5 days postseeding. These basic accomplishments allow us to proceed with the major objectives of this proposal. Specifically, studies examining the influence of hemodynamic shear stress on cell replication, cell to cell and cell to substrate interactions, and platelet and monocyte adherence to endothelium cultured on these potential graft surfaces can now proceed. Finally, these results indicate the feasibility of attaining a totally preendothelialized vascular graft which, potentially, may exhibit superior nonthrombogenicity and patency to currently available small diameter vascular grafts.

3. Human Subjects: No change

4. Vertebrate Animals: No change

5. Publications:

1. Schwartz CJ, Valente AJ, Kelley JL, Sprague EA and Edwards EH. Thrombosis and the Development of Atherosclerosis: Rokitansky Revisited. Seminars in Thrombosis and Hemostasis. 14:189-195, 1988

2. Valente AJ, Delgado R, Metter JD, Cho C, Sprague EA, Schwartz CJ and Graves DT. Cultured Primate Aortic Smooth Muscle Cells Express Both the PDGF-A and PDGF-B Genes, But Do Not Secrete a Mitogenic Platelet-Derived Growth Factor-Like Protein. J Cell Physiol. 136:479-485, 1988

3. Edwards EH, Sprague EA, Schwartz CJ. Low Density Lipoprotein (LDL) Endocytosis. I. Influence of the Multivalent Ligand Cationized Ferritin on Normal and Receptor-Negative Human Fibroblasts. Exp Molec Path. 48:353-372, 1988

4. Sprague EA, Edwards EH, Valente AJ, Suenram CA, Kerbacher JJ and Schwartz CJ. Modified Low Density Lipoprotein (Acetyl-LDL) Endoytosis II: Influence of the Multivalent Ligand, Cationized Ferritin, on Cultured Cells. Exp and Molec Path. 48:373-390, 1988

5. Kelley JL, Rozek MM, Suenram CA and Schwartz CJ. Activation of Human Peripheral Blood Monocytes by Lipoproteins. Am J Path. 130:223-231, 1988

6. Valente AJ, Graves DT, Vialle-Valentin CE, Delgado R and Schwartz CJ. Purification of a Monocyte Chemotactic Factor (SMC-CF) Secreted by Non-Human Primate Vascular Smooth Muscle Cells in Culture. Biochemistry, 27:4162-4168, 1988

7. Kelley JL, Suenram CA, Rozek MM and Schwartz CJ. Influence of hypercholesterolemia and cholesterol accumulation on rabbit carrageenan granuloma macrophage activation. Am J Pathol, 131:539, 1988

8. Sprague EA, Moser M, Edwards EH and Schwartz CJ. Stimulation of Receptor-Mediated Low Density Lipoprotein Endocytosis in Neuraminidase-Treated Cultured Bovine Aortic Endothelial Cells. J. Cell Physiol. 137:251-262, 1988

9. Kelley JL, Suenram CA, Rozek MM, Schaffer SA and Schwartz CJ. Influence of the Acyl-CoA: Cholesterol 0-acyltransferase Inhibitor, CL 277082 on Cholesteryl Ester Accumulation in Rabbit Macrophage-Rich Granulomas and Hepatic Tissue. Biochim et Biophys Acta 960:83-90, 1988

10. Gwyne JT and Schwartz CJ. (eds). A Symposium: Second International Conference on hypercholesterolemia. Examining New Data on Probucol After a Decade of Use. Amer J Cardiol, 62:1B-81B, 1988

11. Schwartz CJ. Introduction - The Probucol Experience: A Review of the Past and a Look at the Future. In a Symposium: Second International Conference on Hypercholesterolemia. Examining New Data on Probucol After a Decade of Use. (JT Gwyne, CJ Schwartz, eds). Am J Cordiol, 62:1B-5B, 1988

12. Schwartz CJ. Advances in Plasma Cholesterol: Key Questions for Clinical Use and Research. Consultant, 28:48-49, 1988

13. Sprague EA, Steinbach BL, Logan SA, Nerem RM and Schwartz CJ. Influence of Shear Stress on Lipoprotein Endocytosis. Proceedings: Biology of the Arterial Wall. "Interaction in the Arterial Wall and Atherosclerosis". CIC Edizioni Internazional: 183-188, 1988

14. Schwartz CJ, Sprague EA, Valente AJ, Kelley JL, Edwards EH and Suenram CA. Inflammatory Components of the Human Atherosclerotic Plaque. Workshop on the Evolution of the Human Atherosclerotic Plaque. Am Heart Assoc, Rockville, Maryland, September 20-23, Springer-Verlag. In press, 1989

16. Schwartz CJ, Sprague EA, Valente AJ, Kelley JL and Edwards, EH. Cellular Mechanisms in the Response of the Arterial Wall to Injury and Repair. Toxic Path. 17: , In press, 1989

17. Edwards EH, Sprague EA, Kelley JL, Kerbacher JJ, Schwartz CJ and Elbein AD. Castanospermine Inhibits the Function of the Low-Density Lipoprotein Receptor. Submitted, 1989

Abstracts:

1. Sprague EA, Edwards EH, Logan S, Schwartz CJ and Nerem RM. Enhanced LDL Receptor Expression in Cultured Arterial Endothelial Cells Exposed to Elevated Fluid-Imposed Wall Shear Stress. Symposium on Engineering Approaches to Atherosclerosis, 1988

2. Schwartz CJ, Sprague EA, Nerem RM and Grover FL. Vascular Healing: Cell Biology and Rheologic Factors. NIH Devices and Technology Branch, Program:33, 1988

3. Prasad ARS, Schwartz CJ. and Sprague EA. Phosphoinositide Metabolism and Low Density Lipoprotein Receptor-Mediated Endocytosis. Circulation 78:484a, 1988

4. Kelley JL, Kerbacher JJ and Schwartz CJ. Purification to Homogeneity of the Acetyl-LDL "Scavenger" Receptor from Rabbit Carrageenan Granulomas. Circulation 78:13a, 1988

5. Sprague EA, Prasad ARS and Schwartz CJ. Role of Signal Transduction in Low Density Lipoprotein (LDL) Receptor-Mediated Endocytosis. J Cell Biol, 107:810a, 1989