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OCA PAD INITIATION - PROJECT HEADER INFORMATION

10/24/96

Active

Project #: E-25-L82  
Center #: 10/24-6-R0165-0A0

Cost share #:   
Center shr #:

Rev #: 0  
OCA file #:  
Work type: RES  
Document: SUBCONT  
Contract entity: GTRC

Contract#: AGR DTD 961003  
Prime #: 5 P01 HL48667-05

Mod #:

Subprojects?: N  
Main project #:

CFDA:  
PE #:

Project unit:  
Project director(s):  
NEREM R M

MECH ENGR  
MECH ENGR

Unit code: 02.010.126  
(404)894-2768

Sponsor/division names: EMORY UNIVERSITY  
Sponsor/division codes: 400

/ ATLANTA, GA  
/ 012

Award period: 960901 to 970831 (performance) 971015 (reports)

Sponsor amount	New this change	Total to date
Contract value	64,116.00	64,116.00
Funded	64,116.00	64,116.00
Cost sharing amount		0.00

Does subcontracting plan apply?: N

Title: MECHANISMS OF ENDOTHELIAL-MONOCYTE ADHESION MOLECULAR REGULATION (YEAR 05).

PROJECT ADMINISTRATION DATA

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1462 CLIFTON ROAD, N.E.  
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ATLANTA, GA 30322

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

ONR resident rep. is ACO (Y/N): N  
NA supplemental sheet  
GIT X

Administrative comments -  
INITIATION OF YEAR 05 SUBGRANT UNDER NIH PRIME GRANT (CONTINUATION OF  
E-25-L08).

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Closeout Notice Date 10-DEC-1997

Project Number E-25-L82

Doch Id 40441

Center Number 10/24-6-R0165-0A0

Project Director NEREM, ROBERT

Project Unit MECH ENGR

Sponsor EMORY UNIVERSITY/ATLANTA, GA

Division Id 5779

Contract Number AGR DTD 961003

Contract Entity GTRC

Prime Contract Number 5 P01 HL48667-05

Title MECHANISMS OF ENDOTHELIAL-MONOCYTE ADHESION MOLECULAR REGULATION  
(YEAR 05)

Effective Completion Date 31-AUG-1997 (Performance) 15-OCT-1997 (Reports)

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

Comments

-

Distribution Required:

Project Director/Principal Investigator	Y
Research Administrative Network	Y
Accounting	Y
Research Security Department	N
Reports Coordinator	Y
Research Property Team	Y
Supply Services Department/Procurement	Y
Georgia Tech Research Corporation	Y
Project File	Y

NOTE: Final Patent Questionnaire sent to PDPI

SPR03

E-25-482

#1

Progress Report on  
Subcontract from Emory University

**Mechanisms of Endothelial-Monocyte  
Adhesion Molecular Recognition**

Prepared by Robert M. Nerem

November 1997

In an effort to determine whether there might be a correlation between fluid shear stress and VCAM-1 expression, human vascular endothelial cells were subjected to both steady and oscillatory fluid flow in a parallel plate flow chamber apparatus, and assayed by a number of molecular biology techniques.

The effects of these fluid environments on both constitutive and cytokine-inducible VCAM-1 gene expression were determined by Northern Analysis. While steady shear stress had no effect on constitutive VCAM-1 gene expression, oscillatory shear stress led to a transient increase of VCAM-1 mRNA levels, peaking at 4 hours and returning to baseline within 12 hours after the onset of flow. Exposure to a steady laminar shear stress of 5 dyn/cm<sup>2</sup> for 24 hours was found to have a "protective" effect on endothelial cells, suppressing subsequent inflammatory cytokine (interleukin-1 b) induction of VCAM-1 mRNA by 95% compared to static controls. Oscillatory shear stress shared this suppressive effect, though much less dramatically, suppressing inflammatory VCAM-1 induction by 40% compared to static controls. This pattern of shear-induced suppression was selective for VCAM-1, as the cytokine-induction of other cell adhesion molecules, ICAM-1 and E-Selectin, was not inhibited by preconditioning to steady or oscillatory shear stress.

The steady shear suppression of inducible VCAM-1 was further investigated in promoter transfection studies and by nuclear protein binding assay. Consistent with mRNA results, the transactivation of two abbreviated homologous VCAM-1 promoter constructs was significantly inhibited in cells preconditioned to a laminar steady shear stress. The binding activity of nuclear factor-kappa B (NF-kB) to its tandem consensus sites on the VCAM-1 promoter was unaltered by shear. Similarly, the transactivation of two known NF-kB-driven promoter constructs remained unaltered by flow preconditioning. Hence, the suppression of VCAM-1 transactivation seems to be through a transcriptional mechanism unaccompanied by any inhibition of NF-kB activity. These results strongly suggest the activation of a repressor protein by steady shear stress which may interact with the VCAM-1 promoter downstream of the NF-kB consensus binding sequences (coordinates -73 and -58).

The transient induction of VCAM-1 gene expression with oscillatory shear stress was also determined to be independent, at least in part, of

NF-kB. Gel shift analysis showed only a modest activation of this binding protein in response to shear.

These results clearly demonstrate that the fluid mechanical environment does indeed play a role in endothelial modulation of this important cell adhesion molecule. Furthermore, the mechanism of VCAM-1 gene regulation is specific to the dynamic character of the flow field (steady vs. oscillatory). Extrapolating to the vessel wall, these effects could at least in part explain the predilection of atherosclerotic lesions for areas of the vessel wall experiencing reversing blood flow.