BIOGRAPHICAL SKETCH

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NAME Lewis Hartley Romer	POSITION TITLE Professor Anesthesiology and Critical Care Medicine, Cell Biology, Biomedical Engineering, and Pediatrics
eRA COMMONS USER NAME (credential, e.g., agency login): LROMER1	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Dartmouth College, Hanover, NH	AB	06/73	Pre-medical
Dartmouth Medical School, Hanover, NH	MD	06/81	Medicine

A. Personal Statement

The long-standing scientific focus of the Romer laboratory is molecular signaling in vascular injury, repair, and regeneration, with a special emphasis on post-translational modification by phosphorylation. Care has been taken over the past two decades to build a multidisciplinary team that incorporates expertise in the biochemistry, molecular biology, and mechanochemical signaling of cell adhesion, the cell biology of cytoskeletal organization, matrix biology, and regenerative medicine. A strong network of international and local collaboration and the outstanding efforts of students from the Biomedical Engineering, and Cell and Molecular Medicine programs at Johns Hopkins have supported a rich intellectually and ethnically diverse environment that has helped the lab to thrive. Current and recent work includes the definition of mechanotransduction pathways in matrix assembly (funded by the National Science Foundation), molecular mechanisms of NO dysregulation and vascular dysfunction in cardiovascular disease (funded by NHLBI, the American Heart Association, the MedImmune Corporation, and a T32 postdoctoral fellowship from the JHU Children's Center), and microvascular tissue engineering (funded by the Posen Foundation). Our multi-level studies focus on vasculopathy in development, pulmonary hypertension, and atherogenesis, and range from transcriptional regulation, to the biochemistry of post-translational modification (phosphorylation, neddylation, and ubiquitination), and proteasomal degradation, to real time imaging of subcellular trafficking, to whole tissue and organism work with a new transgenic mouse line with human HDAC2 expression that is specific to the vascular endothelium.

B. Positions and Honors

Positions and Employment

1981–1984 Pediatric Resident, University of Utah Medical Center
1984–1987 Pediatric Staff Physician Munson Medical Center, Traverse City, MI
1985–1987 Director, NICU and PICU, Munson Medical Center
1987–1989 Pediatric Critical Care Fellow, Childrens' Hosp. of Philadelphia, U. of Pennsylvania
1989–1990 Research Fellow, Wistar Institute and University of Pennsylvania
Research Mentors, Clayton Buck, PhD, and Steve Albelda, MD
1990–1994 Assistant Professor of Pediatrics, University of North Carolina at Chapel Hill
Research Mentor, Keith Burridge, PhD, 1990–1994
1994–1996 Assistant Professor of Pediatrics and Cell Biology, Univ. of North Carolina at Chapel Hill
1996–2000 Associate Professor, Pediatrics, Cell Biology and Anatomy, and Anesthesiology
University of North Carolina at Chapel Hill

2000–2011 Associate Professor, Anesthesiology, Biomedical Engineering, Cell Biology, and Pediatrics Johns Hopkins University School of Medicine, Center for Cell Dynamics

2012–present Professor, Anesthesiology, Biomedical Engineering, Cell Biology, and Pediatrics Johns Hopkins University School of Medicine, Center for Cell Dynamics

2012 - 2016 Director of Professional Development, Division of Pediatric Anesthesiology and Critical Care Medicine (a group including 40 faculty and 20 fellows)

Honors

1974–1977	Rufus Choate Scholar, Dartmouth College
1977	Summa Cum Laude, Dartmouth College
1977	Phi Beta Kappa, Dartmouth College
1976–1977	Senior Fellowship, Dartmouth College
1981	Alpha Omega Alpha, Dartmouth Medical School
1981	Ciba Award for Community Service, Dartmouth Medical School
1991	Faculty Development Award, University of North Carolina at Chapel Hill
1994	Davis Award, American Lung Association, NC Chapter
1995	Jefferson-Pilot Fellowship Award, Univ. of North Carolina at Chapel Hill
1999	Michael Visiting Professorship Department of Molecular Cell Biology Weizmann Institute of Science, Rehovot, Israel
1999–2002	Fogarty Senior International Fellowship
2007	Association of University Anesthesiologists
2007	America's Best Doctors
2010	Selection of work by the Faculty of 1000 (F1000) November 11, 2010 for Biophys J 2010 Nov 3
2014	Selection of work among the most influential research contributions from the Department of ACCM at JHU-SOM – publication on the SAAA website: http://saaahq.org/resources/research-advances/jhmi

C. Contributions to Science

C.i. Interplay Between Non-receptor Tyrosine Kinases and Rho-family GTPases in Focal Adhesion Formation and Cytoskeletal Organization

My experiments in this arena began in the early 1990's as our team in the lab of Keith Burridge characterized the tyrosine phosphorylation of the matrix adhesion complex proteins FAK and paxillin upon integrin-mediated cell adhesion of fibroblasts and endothelial cells to extracellular matrix. This work lent considerable momentum to the definition of tyrosine phosphorylation as a major signaling event in adhesion, motility, and cell cycle control in adherent cells, and catalyzed exploration of this pathway in cellular events from platelet aggregation to apoptosis in cancer cells. Work in my lab next moved to the definition of interactions between the nonreceptor tyrosine kinases FAK and src, and the Rho family GTPase Rac1. This line of inquiry contributed to the understanding of the assembly of multicomponent signaling complexes to focal adhesion turnover and cell motility.

a. Burridge K, Turner CE, **Romer LH**. Tyrosine phosphorylation of paxillin and FAK in cell adhesion. J Cell Biol 119:893–904, 1992. PMID: 1385444
    i. *Featured paper in "Hot Papers," in *The Scientist* October 31, 1994: Burridge K, Turner CE, **Romer LH**.
    ii. *2005 Editorial retrospective on the most influential *JBC* papers: "Pass It On," an interview with Romer L about - Burridge K, Turner,CE, **Romer LH**. *J Cell Biol*. 119:893-904, 1992.
b. **Romer LH**, McLean NV, Turner CT, Burridge K. Tyrosine kinase activity and motility in endothelial cells. Mol Biol Cell 5:349–61, 1994. PMID: 8049526

c. Rajfur Z, Roy P, Otey C, **Romer LH**, Jacobson KA. Chromophore-assisted laser inactivation (CALI) of EGFP fusion proteins: probing the connection between the stress fiber and the focal adhesion. Nat Cell Biol 4:286–93, 2002. PMID: 11912490
d. **Romer LH**, Birukov KG, Garcia JGN. The focal adhesion: Paradigm for a signaling nexus. Circ Res 98:606–16, 2006. PMID: 16543511
e. Chang F, Lemmon CA, Park D, **Romer LH**. FAK potentiates Rac1 activation and localization to matrix adhesion sites: a role for betaPIX. Mol Biol Cell, 2007 Jan;18(1):253-64. PMID: 17093062
f. Chang, F, Lemmon, C, Lietha, D, Eck, M, and **Romer, L.** Tyrosine Phosphorylation of Rac1: A Role in Regulation of Cell Spreading. PLoS ONE, 2011;6(12):e28587. PMID: 22163037
* Featured in *Global Medical Discovery*, August 3, 2012;http://globalmedicaldiscovery.com/key-scientific-articles/tyrosine-phosphorylation-of-rac1-a-role-in-regulation-of-cell-spreading/

C.ii. Mechanochemical Coupling in Extracellular Matrix Assembly

In partnership with Christopher Chen's labs, we pioneered the use of microfabricated PDMS devices to localize adhesion formation to subsets of the ventral cell surface, and to ask questions about subcellular segregation of traction forces and adhesion molecules during matrix assembly and cell adhesion. We defined the transition from compressive to neutral strain at the periphery of fibroblasts as being favorable for fibronectin fibrillogenesis. We then showed that the magnitude and direction of the traction force at a given point of the cell surface is proportional to the first moment of area about that point in the cell, suggesting that contractile forces within the cell act on the entire cytoskeletal network as a single cohesive unit. These findings were presented at international Gordon conferences, and fueled investigations by other investigators into patterns of cellular force and molecular complex assembly that power cell motility and dynamic interactions with extracellular matrix. We contributed our analysis algorithm for cell traction forces as a free download to the scientific community and it has been used widely.

a. Lemmon CA, Sniadecki NJ, Ruiz SA, Tan JL, **Romer LH**, Chen CS. Shear force at the cell-matrix interface: enhanced analysis for microfabricated post array detectors. Mech Chem Biosyst. 2005;2(1):1-16. PMID: 16708468
b. Lemmon, C.A., **Romer, L.H.** Measuring Patterns, Regulation, and Biologic Consequences of Cellular Traction Forces. Gravitational and Space Biology. June; 20(2):19-29, 2007.
c. Lemmon CA, Chen CS, **Romer LH.** Cell Traction Forces Direct Fibronectin Matrix Assembly. Biophysical Journal. 2009 Jan;96(2):729-38. PMID: 1916731
d. Lemmon, CA, and **Romer, LH.** A Predictive Model of Cell Traction Forces Based on Cell Geometry. *Biophysical Letter*, in Biophysical Journal, 2010 Nov 3;99(9):L78-80. PMID: 21044567 * Selection by the Faculty of 1000 (F1000) November 11, 2010

C.iii. Extracellular Matrix Guides Vasculogenesis

In experimental work that began with the assembly of fibronectin-rich 'microtissues' between PDMS posts that were used for the work described above, we investigated the molecular constituency, mechanical properties, spatial orientation, and growth factor content of fibroblast-derived natural matrices. We then asked questions about how these features of naturally derived matrix influenced the growth and morphogenesis of individual endothelial cells and multicellular endothelial tubes within this natural matrix microenvironment. We and others have since used natural matrix platforms to ask further questions about matrix cues that guide tissue repair and morphogenesis.

a. Soucy, PA, and **Romer, LH**. Endothelial Cell Adhesion, Signaling, and Morphogenesis in Fibroblast-Derived Matrix. Matrix Biology. 2009 Jun;28(5):273-83. PMID: 1937550428
b. Soucy, PA, Werbin, J, Heinz, W, Hoh, J, **Romer, LH.** Microelastic properties of lung cell-derived extracellular matrix. Acta Biomaterialia, 2011 Jan;7(1):96-105. PMID: 20656080.
c. Chang F, Lemmon CA, Nilaratanakul V, Rotter V, **Romer L**. Endothelial Matrix Assembly During Capillary Morphogenesis: Insights from Chimeric TagRFP-Fibronectin Matrix. J Histochem Cytochem. 2014 Nov;62(11):774-90. PMID: 25063001

d. Soucy PA, Hoh M, Heinz W, Hoh J, **Romer L.** Oriented matrix promotes directional tubulogenesis. Acta Biomaterialia, 2015, Jan. 11:264-73. PMID: 25219769
e. Serbo JV, Kuo S, Lewis S, Lehmann M, Li J, Gracias, D, **Romer, L.H.** Patterning of Fibroblast and Matrix Anisotropy within 3D Confinement is Driven by the Cytoskeleton. Advanced Healthcare Materials. 2016; 5, 146-158. PMID: 26033825
f. Kwag, HR, Serbo, JV, Korangath, P, Sukumar, S, **Romer, LH**, Gracias, DH. A self-folding hydrogel in-vitro model for ductal carcinoma, Tissue Engineering Part C, 2016; 22, 4, 398-407. PMID: 26831041

C.iv. Endothelial Dysfunction in Vasculopathy, Atherogenesis, and Pulmonary Hypertension

We have demonstrated that arginase 2 is expressed in human endothelial cells and that its activity is increased following exposure to oxidation injury. Inhibition or knockout of arginase increases NO, decreases ROS, improves endothelial function, decreases vascular stiffness and decreases plaque burden in atherogenic mice. Furthermore, we have identified arginase 2 as an early and critical enzyme that is coupled to endothelial dysfunction via the lectin-like OxLDL receptor. Upon exposure to OxLDL, arginase 2 undergoes a rapid decompartmentalization from the mitochondria and activation leading to uncoupling of NOS, endothelial dysfunction and enhanced atherogenesis, a process that is coupled to Lox-1, Rho and the mitochondrial processing peptidase. In addition to this rapid post-translational mechanism leading to arginase activation OxLDL leads to a transcriptional upregulation of arginase. This transcription is regulated by epigenetic mechanisms - HDAC2 is a critical modulator of Arg2 abundance. Overexpression or activation of HDAC2 leads to an increase in Arg2, while knockdown leads to a decrease in Arg2 abundance. Further, HDAC2 is exquisitely regulated by proteasomal degradation pathways that are, in turn, regulated by a novel post-translational event -NEDDylation. OxLDL leads to an increase in NEDDYlation of HDAC2, a decrease in HDAC2 abundance, and an increase in Arg2-mediated endothelial dysfunction - a process that is blocked by either inhibition of the NEDDYlation activating enzyme inhibition, or by enhancement of the de-neddylase, SENP8.

a. Ryoo S, Lemmon C, White R, Nyhan D, Shoukas A, **Romer LH**, Berkowitz DE. Ox-LDL-dependent arginase activation contributes to impaired NO signaling and endothelial dysfunction. *Circ Res*. 2006;99: 951-960. PMID: 17008605 *Accompanying Editorial: PMID: 17068298
b. Ryoo S, Bhunia AK, Chang F, Shoukas A, Berkowitz D*, **Romer LH***. OxLDL-Dependent Activation of Arginase II Is Dependent on the LOX-1 Receptor and Downstream RhoA Signaling. Atherosclerosis, 214(2):279-87, 2011. PMID: 21130456
c. Pandey D, Bhunia A, Oh YJ, Chang F, Bergman Y, Kim JH, Serbo J, Boronina TN, Cole RN, Van Eyk J, Remaley A, Berkowitz DE, **Romer LH**. OxLDL triggers retrograde translocation of arginase 2 via ROCK and mitochondrial Processing Peptidase. *Circ Res*. 2014 June 5 115:450-459. PMID: 24903103 *Accompanying editorial: PMID: 25081132
d. Pandey D, Sikka G, Bergman Y, Kim JH, Ryoo S, **Romer L**, Berkowitz D. Transcriptional regulation of arginase 2 by histone deacetylase 2. *Arterioscler Thromb Vasc Biol*. 2014 May 15 34:1556-1566. PMID: 24833798
e. Pandey D, Hori D, Kim JH, Bergman Y, Berkowitz DE, **Romer LH**. NEDDylation promotes endothelial dysfunction: Role for HDAC2 J Mol Cell Cardiol. 2015 Feb 2;81C:18-22. PMID: 25655932
f. Unegbu, C, Noje, C, Coulson, J, Segal, J, **Romer, L**. *State of the Art Review*: Pulmonary Hypertension Therapy and a Systematic Review on Efficacy and Safety of PDE-5 Inhibitors. *Pediatrics*. August, 2016, In Press.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1r_ClssSZlCk6/bibliography/49375662/public/?sort=date&direction=ascending

Ongoing Research Support

R21 HD090663 (D. Gracias, PI; L. Romer Co-PI) 12/19/16-12/18/18
NICHD
"Self-unfolding RV-PA 3D Printed Conduits"
Develop 3D printing and self-unfolding strategies to create RV-PA conduits that can change their dimensions in a programmed manner that follows infant and childhood growth.

Posen Foundation (L. Romer, PI) 4/1/15 – 3/31/18
"Human Biomimetics"
Development of a human biomimetic microcirculatory platform for drug testing and development for pulmonary hypertension. There is no overlap with the current proposal.

United Therapeutics Corporation (L. Romer, PI; L. Nogee, Co-PI) 9/1/15 – 12/31/17
"Intravenous Remodulin (Treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study"
IRB00050255

CBET-1462184 (L.Romer and D. Gracias, PI's) 7/15/13-7/14/16
NSF NCE to 12/31/16
"Lung Microvascular Development During Dynamic Mechanical Deformation in Matrix Bioblocks"
Investigation of lung microvascular development under conditions of mechanical stretch and interstitial flow delivered by microfluidic systems.

R01 HL089668 (L.Romer and D. Berkowitz (Multi-PI)) 04/1/11-04/30/15
NIH, NHLBI NCE through 12/2016
"Arginase II, A Novel Target in Atherosclerosis".
A study to elucidate the molecular mechanisms of subcellular trafficking and activation of arginase II and their role in atherogenesis.

Completed Research Support (in the past three years)

ALW-GO-MG/10-07, Jack van Loon, Vrije Universiteit, PI 11/2010-11/2014
Netherlands Organisation for Scientific Research, NOW
"Bone Cell Mechanics under Altered Gravity (MechanoCell)".
Role: Co-Investigator

PS-OC (David Gracias, Pilot Project PI; L Romer was Co-I) 9/1/13-7/31/14
Johns Hopkins Physical Sciences in Oncology Center, NIH U54CA141868;

11GRNT7690056 L. Romer (PI) 07/01/11-06/30/13
American Heart Association
"Oxygen Regulation of Three-Dimensional Pulmonary Capillary Morphogenesis".
A study to construct lung-specific 3D model environments with controlled oxygen tensions for the study of pulmonary microvascular development.

MCB-0923661 L. Romer(PI) 7/15/09-7/14/12
NSF
"Molecular Regulation of Matrix Assembly Mechanics"
Investigations into the spatial, mechanical, and molecular regulation of *cellular* traction forces during extracellular matrix assembly.

MedImmune-JHU Contract 90052746 (Multi-PI: L.Romer and D. Berkowitz) 12/1/12-7/31/16
"Biologically Active Monoclonal Antibodies Against the LOX-1 Receptor: Effects on Endothelial Cell Signaling and Nitric Oxide Homeostasis"