**BIOGRAPHICAL SKETCH**

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# eRA COMMONS USER NAME (agency login): mas5bmnih

POSITION TITLE: Robert W. Berliner Professor of Medicine

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

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| --- | --- | --- | --- |
| INSTITUTION AND LOCATION | DEGREE*(if applicable)* | YEAR(s) | FIELD OF STUDY |
| New College, Sarasota, FL Stanford University, Stanford, CA | BAPhD | 19751979 | Chemistry Physical Chemistry |

## A. Personal Statement:

I earned my Ph.D. at Stanford University, where I worked with Harden McConnell on biophysics of model membranes. I then did postdoctoral research with Richard Hynes at MIT, where I learned cell biology studying interactions of fibronectin. As an assistant professor in the Department Physiology and Biophysics at Harvard Medical School, my lab was among the first to demonstrate signaling by integrins and the first to report that integrin-mediated adhesion is required for transmission of signals downstream of growth factor receptors. We were the first to show that Rho family GTPases are signaling intermediates on integrin pathways. In the Dept. of Vascular Biology at Scripps, we were the first to report that cell adhesion is required for survival of endothelial and other cells. We developed the widely used pull down assay for Rho activity and were the first to show that adhesion regulates Rho activity. Our work also identified the first bona fide mechanotransducer for fluid shear stress in endothelial cells, elucidated the role of extracellular matrix proteins in shear responses in atherosclerosis and tested these ideas in animal models of atherosclerosis. We have also invented and used fluorescence based assays for visualizing signaling events in live cells, including sensors that measure molecular tension across specific proteins. Our major goal is to understand the roles of mechanotransduction and integrin signaling in vascular physiology and disease.

##  Positions and Honors Positions and Employment:

1979 - 1982 Postdoctoral Fellow, Department of Biology, Massachusetts Institute of Technology; Advisor: Dr. Richard Hynes

1983 - 1989 Assistant Professor, Department of Cellular and Molecular Physiology, Harvard Medical School

1990 - 1991 Associate Professor, Department of Cellular and Molecular Physiology, Harvard Medical School

1991 - 1995 Associate Professor, Department of Vascular Biology, The Scripps Research Institute 1995 - 1999 Associate Professor with Tenure, Department of Vascular Biology, The Scripps Research

Institute

2000 - 2001 Professor, Department of Vascular Biology, The Scripps Research Institute

2001 - 2002 Head of the Division of Vascular Biology, Department of Cell Biology, The Scripps Research Institute

2002 - 2011 Professor, Departments of Microbiology, Cell Biology and Biomedical Engineering, University of Virginia Investigator of the Mellon Urological Cancer Research Institute and the Cardiovascular Research Center

2011-present Professor of Medicine and Cell Biology, Yale University School of Medicine

2014-present Professor of Biomedical Engineering, Yale University School of Engineering and Applied Science

2016-present Visiting Chair in Cell-Matrix Biology, University of Manchester, UK

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## Honors:

1996-2008 Associate Editor, Molecular Biology of the Cell

1997-2001 Member National Institutes of Health Cell Biology and Physiology I Study Section 2001- Associate Editor, Journal of Cell Biology

2005- Editorial Board, Journal of Cell Science

2008-2011 Member National Institutes of Health Intercellular Interactions Study Section 2008-2011 NAVBO Council

2009 Hayashi Lecturer, Woods Hole MBL Physiology Course 2009 James O Davis Lectureship, University of Missouri 2009-2015 Deputy Chair, Biochemical Journal

2011 Chair for Vascular Cell Biology Gordon Research Conference 2012 Chair for Signaling by Cell Adhesion Receptor Gordon Conference

2012 Named Robert W. Berliner Professor of Medicine, Yale School of Medicine

2013 Andrew P. Somlyo Lecture, Pennsylvania Muscle Institute, University of Pennsylvania 2013 Harold F. Dvorak Plenary Lecture Award, Harvard Medical School

## C.Contributions to Science

1. Discovery of integrin signaling.

In the 1970’s and 80’s, many papers reported that cell adhesion to extracellular matrix regulated cell growth and gene expression but the dominant paradigm was that this occurred through the cytoskeleton. My lab provided the first evidence that integrin-mediated adhesion regulated a cytoplasmic signaling pathway, intracellular pH, through the Na/H antiporter [1, 2]; this work was concurrent with Joan Brugge’s work showing that integrins regulated protein tyrosine phosphorylation in platelets. My lab’s subsequent work provided the first evidence for synergistic effects of integrins and growth factors on signaling pathways and for distinct signals from different integrins (multiple papers, reviewed in [3]). We were also the first to report that integrin signals promote cell survival, preventing a form of apoptosis subsequently named anoikis [4]. This work established the field of integrin signaling and several of the major paradigms therein.

1. Schwartz MA, Both G, Lechene C. Effect of cell spreading on cytoplasmic pH in normal and transformed fibroblasts. Proc Natl Acad Sci U S A. 1989 Jun;86(12):4525-9. PubMed Central PMCID: PMC287303.
2. Schwartz MA, Lechene C, Ingber DE. Insoluble fibronectin activates the Na/H antiporter by clustering and immobilizing integrin alpha 5 beta 1, independent of cell shape. Proc Natl Acad Sci U S A. 1991 Sep 1;88(17):7849-53. PubMed Central PMCID: PMC52401.
3. Meredith JE Jr, Fazeli B, Schwartz MA. The extracellular matrix as a cell survival factor. Mol Biol Cell. 1993 Sep;4(9):953-61. PubMed Central PMCID: PMC275725.

2. Rho GTPases in integrin signaling.

Rho GTPases were originally described as mediators of signals from soluble mediators, indeed, the Hall lab published a paper arguing that integrins did NOT activate Rho family GTPases (Hotchin and Hall, 1995 J. Cell Biol. 131:1857). We provided the first evidence that small GTPases Rho, Rac and Cdc42 are intermediates on integrin pathways that control spreading and cytoskeletal organization [5, 6]. We also developed the Rho pulldown assay and showed directly that integrins control Rho activation [7]. This assay has been very widely used and had major impact on the Rho field. Subsequent work identified a synergistic effect of integrins and growth factor receptors on small GTPases signaling and elucidated the mechanistic basis for these effects [8]. This body of work has served as the foundation for a very large number of studies from other labs on Rho GTPase signaling by different integrins in different biological systems (see Hall 2005 Biochem Soc Trans 33:891 for a review).

1. Chong LD, Traynor-Kaplan A, Bokoch GM, Schwartz MA. The small GTP-binding protein Rho regulates a phosphatidylinositol 4-phosphate 5-kinase in mammalian cells. Cell. 1994 Nov 4;79(3):507-13. PubMed PMID: 7954816.
2. Price LS, Leng J, Schwartz MA, Bokoch GM. Activation of Rac and Cdc42 by integrins mediates cell spreading. Mol Biol Cell. 1998 Jul;9(7):1863-71. PubMed Central PMCID: PMC25428.
3. Ren XD, Kiosses WB, Schwartz MA. Regulation of the small GTP-binding protein Rho by cell adhesion and the cytoskeleton. EMBO J. 1999 Feb 1;18(3):578-85. PubMed Central PMCID: PMC1171150.
4. del Pozo MA, Alderson NB, Kiosses WB, Chiang HH, Anderson RG, Schwartz MA. Integrins regulate Rac targeting by internalization of membrane domains. Science. 2004 Feb 6;303(5659):839-42. PubMed PMID: 14764880.

3. Mechanisms of endothelial fluid shear stress signaling.

By the late 2000’s, fluid shear stress acting on the endothelium was known to be a critical determinant of vascular remodeling and atherosclerosis, and many papers had catalogued effects of flow on gene expression, cytoskeletal organization and signaling pathways, but there was little known about the primary mechanisms of mechanotransduction and little connection between these different findings. We first found that flow triggers conformational activation (conversion to the high affinity state) of endothelial integrins, which then bind to the extracellular matrix (ECM) and a subset of the signals due to flow [9]. We then traced the upstream pathway by which integrins are activated. This work culminated in the identification of a complex consisting of PECAM-1, VE-cadherin and VEGF receptor 2 (VEGFR2) as a mechanosensor for fluid shear stress [10]. This paper has stimulated a great deal of follow up work in many laboratories, mainly to investigate biologic al roles of these receptors in flow dependent remodeling and disease. Subsequent work from my lab directly demonstrated that flow results in an increase in tension across PECAM-1, due not to direct force transmission through the cytoskeleton as originally proposed (Davies PF, 1995, Physiol. Rev. 75:519) but to stimulated attachment of PECAM-1 to vimentin intermediate filaments, which transmit force from myosin [11]. More recently, we discovered that VEGFR3 is also a component of this complex and determines an endothelial fluid shear stress “set point” that governs vessel remodeling [12]. Together, this body of work provided the first coherent model of flow mechanotransduction, developed major insights into mechanisms and into their roles in vascular physiology and disease.

1. .Tzima E, Irani-Tehrani M, Kiosses WB, Dejana E, Schultz DA, Engelhardt B, Cao G, DeLisser H, Schwartz MA. A mechanosensory complex that mediates the endothelial cell response to fluid shear stress. Nature. 2005 Sep 15; 437(7057):426-31. PubMed PMID: 16163360.
2. Conway DE, Breckenridge MT, Hinde E, Gratton E, Chen CS, Schwartz MA. Fluid shear stress on endothelial cells modulates mechanical tension across VE-cadherin and PECAM-1. Curr Biol. 2013 Jun 3; 23(11):1024-30.; PubMed Central PMCID: PMC3676707.
3. Baeyens N, Nicoli S, Coon BG, Ross TD, Van den Dries K, Han J, Lauridsen HM, Mejean CO, Eichmann A, Thomas JL, Humphrey JD, Schwartz MA. Vascular remodeling is governed by a VEGFR3-dependent fluid shear stress set point. Elife. 2015 Feb 2;4. PubMed Central PMCID: PMC4337723.
4. Baeyens N., Larrivée B, Ola R.,Hayward-Piatkowskyi B., DubracA., Huang B., Ross TD, Coon BG, Min E, TsarfatiM, Tong H, Eichmann A and Schwartz MA. Defective fluid shear stress mechanotransduction mediates hereditary hemorrhagic telangiectasia (HHT). 2016 J. Cell Biol. *In press*.

4. Modulation of flow signaling by extracellular matrix.

The finding that flow activated integrins, which then bind ECM and signal, raised the possibility that the ECM could modulate flow signaling. We discovered that laminin/collagen IV basement membrane typical of unperturbed, stable vessels confers anti-inflammatory flow signaling, whereas fibronectin, which is secreted and assembled in vessels undergoing angiogenesis, inflammation or remodeling, renders flow signaling inflammatory [13-15]. Functional genetic studies in mice and large scale GWAS studies in humans support the idea that ECM proteins are important determinants of atherosclerosis (Tan, 2004, Blood 104:11; Rohwedder, 2012, EMBO Mol. Med. 4:7; Schunkert 2011 Nat. Genet. 43:333).

1. Orr AW, Sanders JM, Bevard M, Coleman E, Sarembock IJ, Schwartz MA. The subendothelial extracellular matrix modulates NF-kappaB activation by flow: a potential role in atherosclerosis. J Cell Biol. 2005 Apr 11; 169(1):191-202. PubMed Central PMCID: PMC2171897
2. Orr AW, Stockton R, Simmers MB, Sanders JM, Sarembock IJ, Blackman BR, Schwartz MA. Matrix-specific p21-activated kinase activation regulates vascular permeability in atherogenesis. J Cell Biol. 2007 Feb 26; 176(5):719-27. PubMed Central PMCID: PMC2064028.
3. Yun S, Budatha M, Dahlman JE, Coon BG, Cameron RT, Langer R, Anderson DG, Baillie G, Schwartz MA. [Interaction between integrin α5 and PDE4D regulates endothelial inflammatory signalling.](http://www.ncbi.nlm.nih.gov/pubmed/27595237) Nat. Cell Biol. 2016 epub Sept 5. PMCID in process.

5. Development of a molecular tension sensor.

While forces across proteins are widely thought to induce changes in function that mediate mechanotransduction throughout biology, the inability to measure these forces was a major bottleneck for progress. We therefore developed a calibrated, FRET-based sensor that reports tension across specific proteins and used to determine absolute forces across vinculin in focal adhesions and their role in adhesion strengthening [16]. We also used it to study the components of the flow sensing apparatus [11], as discussed above. Other groups have now used it to study mechanical forces in a wide range of systems and organisms (Borghi, 2012, PNAS 109:12568; Cai, 2014 Cell 157:1146; Krieg, 2014 Nat Cell Biol 16:224, to name a few).

1. Grashoff C, Hoffman BD, Brenner MD, Zhou R, Parsons M, Yang MT, McLean MA, Sligar SG, Chen CS, Ha T, Schwartz MA. Measuring mechanical tension across vinculin reveals regulation of focal adhesion dynamics. Nature. 2010 Jul 8;466(7303):263-6. PubMed Central PMCID: PMC2901888.
2. Kumar A, Ouyang M, Van den Dries K, McGhee EJ, Tanaka K, Anderson MD, Groisman A, Goult BT, Anderson KI, Schwartz MA. [Talin tension sensor reveals novel features of focal adhesion force transmission and mechanosensitivity.](http://www.ncbi.nlm.nih.gov/pubmed/27161398) 2016 J.Cell Biol. *In press.*

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[&direction=asc ending](http://www.ncbi.nlm.nih.gov/myncbi/martin.schwartz.1/bibliography/40899383/public/?sort=date&amp;amp%3Bdirection=ascending)