BIOGRAPHICAL SKETCH

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NAME: Spudich, James A.

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POSITION TITLE: Professor of Biochemistry

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Illinois, Champaign-Urbana	B.S.	06/63	Chemistry
Stanford University, Stanford	Ph.D.	01/68	Biochemistry
Stanford University, Stanford	Postdoctoral	01/69	Genetics
MRC Lab Molecular Biology, Cambridge, England	Postdoctoral	01/71	Structural Biology

A. Personal Statement

Our long-term goal is to understand how enzymes use specific structural elements to carry out their exquisite roles. We have focused on the myosin family of enzymes, which do much more than simply catalyze the conversion of a substrate to a product. The ATPase activity of myosin molecular motors is precisely coupled with binding to and release from actin filaments along which they move, as well as to a conformational change that provides force and directionality for movement. Understanding these structure-function relationships is a prerequisite to uncovering the effects of disease-causing mutations in the genes encoding these molecular motors. An important component of our projects is technology development, which has been a hallmark of our work throughout the years, starting with the establishment of the first quantitative in vitro motility assays. These technologies have important applications far beyond the field of myosin and even molecular motors. Underlying all of our specific goals is our general goal of understanding the relationships between the chemistry at the active site and the structural dynamics of the myosin molecule. The lever arm swing of myosin, coupled to changes in the nucleotide occupancy of the active site, is a particularly good experimental system to study chemomechanical coupling.

My laboratory is well equipped to measure the relevant parameters of interest. Over the last 40 years, we have used an interdisciplinary and multifaceted approach to elucidate the molecular basis of energy transduction by the myosin family of molecular motors. We have developed both *in vitro* motility assays and single molecule approaches to assess the function of mechano-enzymes such as myosin. Thus, we developed a dual-beam optical trap assay to measure the stroke size and the maximum force that single molecules of myosin can produce, the SHREC method of dual fluorescent molecule localization, and the use of gold nanoparticles for examining myosin structural dynamics.

I have a broad background, with specific training in chemistry, biochemistry, biophysics, molecular genetics, genetics and structural biology. My leadership experiences include heading a laboratory of average size of about 12 researchers for more than 40 years. I have been Chairman of two departments at Stanford, and was Cofounder and first Director of the Interdisciplinary Program in Bioengineering, Biomedicine and Biosciences (Bio-X) at Stanford. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, and of the importance of flexibility and innovation during the process of the execution of the experimental plan. Perhaps most importantly, I have been able to continually attract superb graduate students and postdoctoral fellows, and my

current team is no exception. My current research focuses on hypertrophic and dilated cardiomyopathies, which affect 1 in 500 people. These diseases are debilitating and can lead to sudden death. Our focus is on the contractile machinery, studied at the molecular and single cardiomyocyte levels.

B. Positions and Honors

Positions and Employment

1971-1977	Assistant, Associate and Full Professor, Department of Biochemistry & Biophysics, University of California, San Francisco
1977-1992	Professor, Department of Structural Biology, Stanford University School of Medicine (Chairman from 1979-1984)
1989-2011	Professor, Department of Developmental Biology, Stanford University School of Medicine
1992-	Professor, Department of Biochemistry, Stanford University School of Medicine (Chairman from 1994-1998)
1998-2002	Co-Founder and first Director, Interdisciplinary Program in Bioengineering, Biomedicine and Biosciences – Bio-X, Stanford University
2005-	Visiting Faculty in the National Center for Biological Sciences and the Department of Biological Sciences of the Tata Institute of Fundamental Research, Bangalore, India

Other Experience and Professional Memberships

1971-	Member, American Society of Biological Chemistry and Molecular Biology
1975-	Member, The American Society for Cell Biology
1980-	Member, Biophysical Society
1984-1994	Associate Editor, Annual Review of Cell Biology
1984-1989	Member, Research Committee National American Heart Association
1985-1990	Chair, NIH Peer Review Committee
1986-1990	Member, Searle Scholars Program Advisory Committee
1987	Council, American Society for Cell Biology
1988-1989	Chairman Scientific Program Steering Committee of the National American Heart Association
1989	President, The American Society for Cell Biology
1990	Chairman, Searle Scholars Program Advisory Committee
1991-1996	Principal Center Scientist, Stanford AHA Bugher Center Grant in Molecular Biology
1992	Member, Carnegie Mellon Advisory Board
1994-	External Scientific Member of Max-Planck-Institute für Biochemie in Martinsried bei München
1994-1998	Senior Editor, Annual Review of Cell and Developmental Biology
1997-2000	Member, Max Planck Institute Advisory Board, Dortmund
2000-2008	Member, National Center for Biological Sciences Advisory Board, Bangalore
2006-2014	Member, ASCB International Affairs Committee
2010-2013	Chair, ASCB International Affairs Committee

Honors

1976	Dreyfus Teaching and Research Scholar
1978	Guggenheim Fellow
1987	Named the "Douglass M. and Nola Leishman Professor of Cardiovascular Disease"
1991	American Heart Association Basic Research Prize
1991	Elected Member of the National Academy of Sciences
1991	Alexander von Humboldt Research Award
1991	NIH Merit Award
1994	External Scientific Member of Max-Planck-Institute in Martinsried bei München
1995	Biophysical Society Lifetime Research Career Award
1996	Lewis S. Rosenstiel Award for Outstanding Research Achievement in the Field of Basic Medical Studies
1996	1997 Award for the Chemistry of Biological Processes of the Division of Biological Chemistry of the American Chemical Society
1997	Elected Fellow of the American Academy of Arts and Sciences
2001	Elected Fellow of the American Association for the Advancement of Science
2005	Biophysics Society Award for Outstanding Investigator in the Field of Single Molecule Biology

2011 E.B. Wilson Medal, the American Society for Cell Biology
2012 Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences
2012 Wiley Prize
2012 Albert Lasker Basic Medical Research Award
2013 Ahmed H. Zewail Award Gold Medal
2013 Massry Prize

C. Contributions to Science

1. My early work was on bioluminescence in *V. fischeri*, sporulation in *B. subtilis*, deletion frequencies in the tryptophan operon of *E. coli*, and the first elucidation of the structure of the actin-tropomyosin-troponin complex from muscle, in that order. This was excellent training ground in the areas of chemistry, biochemistry, genetics and structural biology, and prepared me for my interdisciplinary approach to studies of the actin-myosin contractile system in muscle and non-muscle cells for the next four decades.
    a. Spudich, J.A., and Hastings, J.W. (1963). Inhibition of the Bioluminescent Oxidation of Reduced Flavin Mononucleotide by 2-Decenal. *J. Biol. Chem. 238*:3106-3108. PMID: 14081933.
    b. Spudich, J.A., and Kornberg, A. (1968). Biochemical Studies of Bacterial Sporulation and Germination. VI. Origin of Spore Proteins. *J. Biol. Chem. 243*:4588-4599. PMID: 4971699.
    c. Spudich, J.A., Horn, V., and Yanofsky, C. (1970). On the Production of Deletions in the Chromosome of *Escherichia coli*. *J. Mol. Biol. 53*:49-67. PMID: 4922221.
    d. Spudich, J.A., Huxley, H.E., and Finch, J. (1972). Regulation of Skeletal Muscle Contraction. II. Structural Studies of the Interaction of the Tropomyosin-Troponin Complex with Actin. *J. Mol. Biol. 72*:619-632. PMID: 4349760.

2. Important contributions from my laboratory over many years derived from our development of *Dictyostelium discoideum* as a model system to study non-muscle cell movements and changes in cell shape. Our discovery of efficient homologous recombination in this organism allowed us to use a molecular genetics approach to prove genetically that myosin II is required for cytokinesis, but, interestingly, not for cell migration as had been thought.
    a. Clarke, M., and Spudich, J.A. (1974). Biochemical and Structural Studies of Actomyosin-Like Proteins from Nonmuscle Cells. I. Isolation and Characterization of Myosin from Amoebae of *Dictyostelium discoideum*. *J. Mol. Biol. 86*:209-222. PMID: 4278009.
    b. De Lozanne, A., and Spudich, J.A. (1987). Disruption of the *Dictyostelium* Myosin Heavy Chain Gene by Homologous Recombination. *Science 236*:1086-1091. PMID: 3576222.
    c. Egelhoff, T.T., Lee, R.J., and Spudich, J.A. (1993). *Dictyostelium* Myosin Heavy Chain Phosphorylation Sites Regulate Myosin Filament Assembly and Localization *In Vivo*. *Cell 75*:363-371. PMID: 7691416.
    d. Zang, J.H. and Spudich, J.A. (1998). Myosin II Localization during Cytokinesis Occurs by a Mechanism That Does Not Require Its Motor Domain. *Proc. Natl. Acad. Sci. USA 95*:13652-13657. PMCID: PMC24874.

3. My laboratory is probably best known for our development of in vitro motility assays for the field of molecular motors. We used these assays to show that the globular head of myosin, known as subfragment-1, or S1, is the motor domain of the myosin molecule, and, together with molecular genetic approaches using non-muscle myosins, we provided early strong functional evidence that the light chain (LC) binding region of the S1 acts as a swinging lever arm during the chemo-mechanical coupling.
    a. Spudich, J.A., Kron, S.J., and Sheetz, M.P. (1985). Movement of Myosin-Coated Beads on Oriented Filaments Reconstituted from Purified Actin. *Nature* 315:584-586. PMID: 3925346.
    b. Kron, J., and Spudich, J.A. (1986). Fluorescent Actin Filaments Move on Myosin Fixed to a Glass Surface. *Proc. Natl. Acad. Sci. USA* 83:6272-6276. PMCID: PMC386485.
    c. Toyoshima, Y.Y., Kron, S.J., McNally, E.M., Niebling, K.R., Toyoshima, C., and Spudich, J.A. (1987). Myosin Subfragment-1 Is Sufficient to Move Actin Filaments In Vitro. *Nature* 328:536-539. PMID: 2956522.
    d. Uyeda, T.Q.P., Abramson, P.D., and Spudich, J.A. (1996). The Neck Region of the Myosin Motor Domain Acts as a Lever Arm to Generate Movement. *Proc. Natl. Acad. Sci. USA* 93:4459-4464. PMCID: PMC39560.

4. Using the physics of laser trapping, we developed a dual-beam laser trap for myosin studies, which helped usher in the field of single molecule biology. We solved a longstanding debate on the step-size of myosin by showing that a single molecule of muscle myosin has a step size of ~10 nm and that the intrinsic force produced by the motor is a few piconewtons. We developed several further single molecule methods and applied them to studies of myosin V and myosin VI. Those studies firmly established the swinging lever arm mechanism of myosin movement.
    a. Finer, J.T., Simmons, R.M., and Spudich, J.A. (1994). Single Myosin Molecule Mechanics: Piconewton Forces and Nanometre Steps. *Nature* 368:113-119. PMID: 8139653.
    b. Churchman, L.S., Ökten, Z., Rock, R.S., Dawson, J.F., and Spudich, J.A. (2005). Single Molecule High-resolution Colocalization of Cy3 and Cy5 Attached to Macromolecules Measures Intramolecular Distances through Time. *Proc Natl Acad Sci USA 102*:1419-1423. PMCID: PMC545495.
    c. Bryant, Z., Altman, D. and Spudich, J.A. (2007). The Power Stroke of Myosin VI and the Basis of Reverse Directionality. *Proc **N**atl Acad Sci USA 104*:772-777. PMCID: PMC1713167.
    d. Dunn, A. and Spudich, J.A. (2007). Dynamics of the Unbound Head during Myosin V Processive Translocation. *Nature Struct Mol Biol*. *14*: 246-248. PMID: 17293871.

5. Our research emphasis has shifted away from myosins V and VI, which are now relatively well understood, and back to muscle myosin - this time to the clinically most important myosin motor, human β-cardiac myosin. We have used a mammalian expression system not only to characterize the wild type forms of human α- and β-cardiac myosin, but we have also initiated studies to understand how hypertrophic (HCM) and dilated (DCM) mutations in β-cardiac myosin affect its biomechanical function and lead to these clinically important heart muscle diseases. Our goal is a complete analysis of the battery of parameters that feed into power output of the sarcomere, using the human form of the β-cardiac myosin.

    a. Sommese, R.F., Sung, J., Nag, S., Sutton, S., Deacon, J.C., Choe, E., Leinwand, L.A., Ruppel, K., and Spudich, J.A. (2013). Molecular Consequences of the R453C Hypertrophic Cardiomyopathy Mutation on Human β-cardiac Myosin Motor Function. *Proc Natl Acad Sci USA*. *110*:12607-12612. PMCID: PMC3732973.
    b. Spudich, J.A. (2015). The Myosin Mesa and a Possible Unifying Hypothesis for the Molecular Basis of Human Hypertrophic Cardiomyopathy. *Biochem Soc Trans*. *43*:64-72. PMCID: PMC4349527.
    c. Aksel, T., Choe Yu, E., Sutton,S., Ruppel, K.M. and Spudich, J.A. (2015). Ensemble Force Changes that Result from Human Cardiac Myosin Mutations and a Small-Molecule Effector. *Cell Reports 11:*1–11. PMCID: PMC4431957.
    d. Nag, S., Sommese, R.F., Ujfalusi, Z., Combs, A., Langer, S., Sutton, S., Leinwand, L.A., Geeves, M.A., Ruppel, K.M. and Spudich, J.A. (2015). Contractility Parameters of Human β-cardiac Myosin with the Hypertrophic Cardiomyopathy Mutation R403Q Show Loss of Motor Function. *Sci Adv 1*(9):e1500511. doi: 10.1126/sciadv.1500511. PMID: 26601291.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/james.spudich.1/bibliograpahy/40598994/public/?sort=date&direction=descending