KAINOMYX

Biosketch

James Spudich, PhD(biochemistry/biophysics/cell biology)

James Spudich, Douglass M. and Nola Leishman Professorof Cardiovascular Disease at Stanford University, received his B.S. in chemistry from the University of Illinois in 1963 and his Ph.D. in biochemistry from Stanford in 1968. He did postdoctoral work in genetics at Stanford and in structural biology at the MRC Laboratory in Cambridge, England. From 1971 to 1977 he was Assistant, Associate, and Full Professor in the Department of Biochemistry and Biophysics, University of California, San Francisco. In 1977, he was appointed Professor in the Department of Structural Biology at Stanford University, and served as Chairman of the Department from 1979-1984. Since 1992 he has been Professor in the Department of Biochemistry and served as Chairman from 1994-1998. From 1998 to 2002, he was Co-Founder and first Director of the Stanford Interdisciplinary Program in Bioengineering, Biomedicine and Biosciences called Bio-X. He is also an Adjunct Professor at the National Center for Biological Sciences, Tata Institute of Fundamental Research and InStem in Bangalore, India.

Spudich's industry experience includes serving on the Discovery Board of Smith-Kline Beecham (now GSK) from 1996-1998. In 1998 he co-founded Cytokinetics, focused on treatments for diseases characterized by compromised muscle function like amyotrophic lateral sclerosis and heart failure, and he has served on the Scientific Advisory Board of Cytokinetics from 1998-present.Spudich also served on the Board of Directors of Cytokinetics from 1998-2012. Cytokinetics has a small molecule activator (Omecamtivmecarbil) of cardiac muscle for heart failure patients in phase III clinical trials, and a small molecule activator (Tirasemtiv) in phase II clinical trials for skeletal muscle diseases such as ALS. These therapeutics are based directly on Spudich's work.

Over the last decade Spudich has been devoted to understanding the molecular basis of hypertrophic cardiomyopathy, a genetic disease that affects 1 out of 500 individuals and leads to sudden death. On the basis of that work he co-founded MyoKardia in 2012. MyoKardia is based on Spudich's work on this important monogenic disease, and phase III clinical trials with a cardiac inhibitor (Mavacamten) holds great promise for small molecule therapeutic intervention for this deadly disease.

Spudich's research on actin-myosin-based biology spans five decades. From his 3D reconstructions from electron micrographs in 1970, he was the first to propose the steric blocking mechanism for tropomyosin-troponin-based Ca^{2+} regulation for muscle contraction. His laboratory created the first quantitative in vitro motility methods with purified proteins to demonstrate that myosin moves along actin filaments, and at velocities comparable to those of muscle contraction. Using these in vitro motility methods, his laboratory established that the head of the myosin molecule is the motor domain, eliminating many proposed mechanisms for muscle contraction and focusing attention on the myosin head domain. His laboratory then

created a laser trap method for single molecule analysis and demonstrated piconewton forces and step sizes of ~10 nm by a single myosin molecule acting on a single actin filament. These experiments helped usher in the new field of single molecule chemistry, biochemistry and biophysics, an example of Spudich's impact in fields in addition to his specific discipline. Further, using the dual beam laser trap for single molecule analysis, his laboratory showed that non-muscle myosins V and VI are both processive motors, and provided the definitive demonstrations of the swinging lever arm mechanism for myosin movement.

In the course of his work, his laboratory discovered and developed homologous recombination in *Dictyostelium*, and used it to knockout the single copy myosin II heavy chain gene, providing genetic proof that the myosin II motor is required for cytokinesis and cell polarization. Importantly, mutagenizing specific regions of the myosin molecule and expressing the mutagenic myosins in *Dictyostelium* allowed him to biochemically and biophysically characterize in detail the chemistry of the myosin molecule.

Over the last decade, his laboratory has focused on the molecular underpinnings of hypertrophic cardiomyopathy (HCM), how increases in power output of the heart due to missense mutations in human ß-cardiac myosin lead to clinical hyper-contractility. Work from his laboratory has overturned conventional views by showingthat HCM mutations shift the equilibrium from a sequestered 'off-state' of myosin heads to their 'on-state', leading to the hyper-contractility seen clinically.

Spudich has given more than 50 named lectureships and keynote addresses, including the Keynote Lecture for the David L. Lacey Award, Amgen; DuPont Lavoisier Lecture; Cori Lecture, Washington University; Plenary Lecture, Madrid International Congress on Cell Biology; the Pauling Lecture, Stanford; the Paul Dudley White Lecture, Mass General Hospital of Harvard University; the DeWitt Stetten, Jr. Lecture, NIH; the Meyerhof Lecture, Heidelberg; the Keith R. Porter Lecture, ASCB; the Hans Neurath Lecture, University of Washington; the National Lecture, Biophysical Society; the Mayer Lecture, MIT;Albert Szent-Györgyi Lecture, Eötvös University, Budapest; Vanderbilt Flexner Discovery Lecture; and the Robert J. Lefkowitz MD Distinguished Lecture, Duke University.

Spudich was a recipient of a Guggenheim Fellowship in 1978. He was elected to the National Academy of Sciences in 1991. He is a member of the American Academy of Arts and Sciences, and the American Association for the Advancement of Science. Spudich has received numerous awards, including the American Heart Association Basic Research Prize; the Biophysical Society Lifetime Research Career Award; the Lewis S. Rosenstiel Award for Outstanding Research Achievement in the Field of Basic Medical Studies; the Biophysical Society Award for Outstanding Investigator in the Field of Single Molecule Biology; the E.B. Wilson Medal; the Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences; the Wiley Prize in Biomedical Sciences;the University of Illinois Alumni Award in 2018; and in 2012, he was a recipient of the Albert Lasker Basic Medical Research Award.