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## 2000

### James Spudich

For Jim Spudich the introduction to science came in the form of a chemistry set he received as a present when he was five years old. "I remember being old enough to open the box!" he recalls of his earliest memory. "My life was a series of such sets which grew in size to the laboratory that I now have at Stanford."

Spudich's father, Anthony Spudich, is a retired, self-taught electrical engineer who will be 90 next year; together with his mother, Martha Spudich, they shared the goal of sending their children to college and allowing them to pursue any field that provided them with satisfaction and fulfillment. "My brother John and his wife Elena are very successful scientists at the University of Texas, elucidating the molecular basis of function of the all important rhodopsin family of molecules," Spudich explains. "We were both allowed to pursue the natural wonder of biology."

Born in Collinsville, Illinois, Spudich and his family moved to Phoenix, at about the same time as the arrival of the chemistry set. The family returned to Illinois as Spudich entered the seventh grade. He remained in his home state, attending the University of Illinois, Champaign-Urbana, where he earned his bachelor's degree in Chemistry in 1963.

For graduate school, Spudich moved to Stanford in 1963, where he fell in love with Northern California and never left. Apart from the famous climate and natural beauty, Spudich found the San Francisco Bay Area to be rich with science due to the proximity of Stanford, UCSF and UC Berkeley.

Working with Nobel laureate Arthur Kornberg, Spudich earned his PhD in Biochemistry from Stanford in 1968. Kornberg is known for his discovery of DNA polymerase. "That was very far away from what I do now," reflects Spudich, "but Arthur and the Biochemistry Department were then and remain world-renowned for advances in biochemistry and for training young people in this discipline. Having had the good fortune of learning biochemistry from the masters, I then sought first hand experience in genetics and structural biology for my postdoctoral experiences."

Spudich spent a year doing postgraduate work in molecular genetics at Stanford in the laboratory of Charles Yanofsky, followed by two years at the MRC Laboratories in Cambridge, England "to learn how to think about structure. I felt that I had a good working knowledge of biochemistry and genetics, but I did not feel comfortable Spudich worked in Cambridge with Hugh Huxley on a project that involved close collaboration with Aaron Klug's group.

Spudich recalls that the MRC was the "mecca" for structural biology at that time thinking about structural biology. It seemed clear that the future was going to require the mixing of these three different disciplines."

In 1971, Spudich joined the faculty of the University of California, San Francisco in the Department of Biochemistry & Biophysics. He remained at UCSF, working his way through the faculty ranks, until in 1977 he returned to Stanford and in 1979 he became Chair of the Department of Structural Biology at Stanford Medical School, a position he held until 1984. Spudich later served a term as Chair of the Department of Biochemistry, where he continues his research program.

Since 1971, Spudich's scientific research has focused on two areas, both involving the molecular motor myosin. "The focus all these years since 1971 has been on two fronts: how the myosin family of molecular motors actually work as little machines, and what role they play in vivo. We have incorporated many different disciplines into our research to answer those questions and have also found it necessary to devise totally new ways of approaching our research as needed (for example, the invention of in vitro motility assays for measuring movement under a microscope outside the cell). We put a lot of effort into that from 1971 on and eventually came up with a number of ways of quantitating movement with purified proteins. Having such assays, we were able to simplify the muscle system, find out how many proteins from the muscle cell you really need to get movement at in vivo velocities of contraction, and what part of the myosin molecule is the motor domain. We were able to pare it down and show that it's the head domains that are the motor domains, which eliminated a number of theories of how actomyosin may contract. Some of the theories involved other parts of the molecule and we showed you don't need those domains at all."

As it became clear that everything that cells do is controlled by a battery of about 100 motors and a wide variety of cytoskeletal components, Spudich, Ron Vale, Larry Goldstein and James Sabry began to get together every few weeks to talk about targeting the cytoskeleton for drug discovery in relation to cancer therapy, cardiovascular problems, and other diseases.

Spudich muses that, “the four of us strongly believed that many diseases are likely to be controllable by specific drug therapy against a cytoskeletal target and may involve much more specific drug therapy than is available today. So if there is a process-specific and/or tissue-specific motor or other cytoskeletal target, then a small molecule inhibitor or activator of that specific target could be a very special therapeutic agent. We continue to believe that the cytoskeleton offers an excellent opportunity for cell-specific and process-specific drug therapy without impairing other physiological functions.”

Seeing an opportunity to develop discovery in this area, Spudich, Sabry, Vale and Goldstein co-founded Cytokinetics in 1998. “Cytokinetics got started because it became clear that the existing biotech companies were all looking at therapeutic targets that were cell surface receptors, signaling pathways, and so on. None of them were based on the large array of cytoskeletal proteins that interact in an integrated way to carry out the functions in the cell that these signals are controlling.”

As if co-founding a company was not enough, Spudich’s latest venture is the new Stanford Bio-X Program. Spudich explains that, “the goal of the Bio-X Program is to break down whatever barriers exist among the disciplines of physics, biology, chemistry, engineering and clinical medicine to allow investigators at all levels—students, postdocs, faculty—to interact with one another on a daily, even hourly, basis.”

To foster those interactions Stanford is creating the Clark Center, 225,000 square feet of space to house 45 faculty from three different schools representing the various disciplines. The Center will allow faculty to work in a very direct, interactive way “so that they learn each other’s languages.” Spudich explains, “The goal is to promote interdisciplinary interaction which can’t thrive under the existing structural way we do things, with each disciplinary group in their own building. Also, there is too much separation between the clinical science world and the basic science world, and we intend to enhance those interactions significantly.”

Spudich is also passionate about flying. Since learning to pilot a plane at Friday Harbor in 1975, Spudich has flown regularly. “I find flying a wonderful way to clear my head, and how can one not experience that which probably represents one of the most incredible advances of the 20th century? In all of evolution, until relatively recently, man had never left the earth to experience the freedom of space,” Spudich reflects.

Spudich met his wife, Annamma, while at the Marine Biological Laboratory at Woods Hole (see the February, 1994 ASCB Newsletter for the Member Profile on Anna Spudich). They were married in 1964. Anna Spudich, a native of southern India, has a Ph.D. in Biological Sciences from Stanford and is a scholar of Ayurvedic Medicine and other alternative medicines.

The Spudichs are the parents of two daughters: Rani earned her MD from Yale, and after two years of residency training in surgery, is currently working for a health-related dot com. Serena earned her MD from UCSF and is currently finishing her residency in neurology at Harvard. Serena recently gave birth to the Spudichs’ first grandchild, Indra Shoshana.