THE FORTIETH ANNUAL
VERNA AND MARRS MCLEAN
LECTURES IN BIOCHEMISTRY

SIR ALAN R. FERSHT, FRS, FMedSci
ROGER Y. TSIEN, Ph.D.

February 9, 2012
Cullen Building Main Auditorium
BAYLOR COLLEGE OF MEDICINE
Verna and Marrs McLean
Department of Biochemistry & Molecular Biology

Verna and Marrs McLean
Nobel Laureate Lecturers in Biochemistry

Paul Berg and Hans Krebs
Bengt Samuelson
Walter Gilbert and Francis H.C. Crick
Arthur Kornberg
Salvador E. Luria
D. Carleton Gajdusek
George E. Palade and Sydney Brenner
J. Michael Bishop
James D. Watson
Thomas R. Cech
Aaron Klug and David Baltimore
Max F. Perutz
Joseph L. Goldstein and Michael S. Brown
Paul Nurse
Phillip A. Sharp
Christine Nüsslein-Volhard
Richard Axel and Harold E. Varmus
Leland H. Hartwell and Martin Rodbell
H. Robert Horvitz
Mario R. Capecchi
Peter C. Agre and Eric F. Wieschaus
Jack W. Szostak
Roger Y. Tsien

The Department was established to promote an essential medical science focused on the knowledge of chemical reactions in the living cell, and to provide students with sound scientific principles on which to base their clinical experience. It has since expanded to provide graduate education and research training leading to a Ph.D. degree. The research programs in the department cover a broad spectrum of basic science aimed at advancing knowledge in many areas, from protein function at an atomic level to systems biology. The diversity of research topics and the collaborative spirit of a world-class faculty provide a vibrant training environment for students and postdoctoral trainees.

The department supports the National Center for Macromolecular Imaging, which provides a resource for the structural determination of proteins and large protein complexes through cryoelectron microscopy. It has assumed a national leadership role in the scientific community through numerous collaborations and continuous innovation.

History of the Lectures

The Verna and Marrs McLean Lecture series were inaugurated in 1972 by Salih J. Wakil, Distinguished Service Professor and Chairman Emeritus, in honor of an outstanding Texas family for their generous support of the department. Verna and Marrs McLean shared a philosophy of civic and humanitarian responsibility and a keen commitment to education. Although they were personally generous and supported many philanthropic causes, they believed that their greatest contribution was to set an example that encouraged others to make equally strong commitments. This tradition has been maintained by their children and grandchildren, as exemplified by the recent endowment of the Ruth McLean Bowman Bowers Professorship, which will support a new faculty member in the department, as well as the establishment of the new Ruth McLean Bowman Bowers “Excellence in Research” award.

Program

2:00 “Tumour Suppressor P53 - from Structure to Drug Discovery”
Sir Alan R. Fersht, FRS

3:10 Reception/Break

3:40 “Breeding and Building Molecules to Spy on Cells and Disease Processes”
Roger Y. Tsien, Ph.D.
Sir Alan R. Fersht attacks mechanisms of enzyme catalysis and protein folding like the chess master he almost became. Born in London, he claims always to have been a scientist, one who “likes to learn unsystematically from experiment, experience, and osmosis.” He tells of dismantling a flashlight as a young boy, working out the electrical connectivity, and constructing a circuit to light a Christmas crib. Later, he persuaded his father to buy chemicals and glassware to support his chemistry experiments. At Sir George Monoux Grammar School, he was exposed to a perfect environment for inquisitive boys: no pressure to work and little homework. He found he loved chemistry and physics “because with minimal knowledge, one could solve problems based on general principles and logical reasoning.” His free time was spent playing chess, where he learned the value of short-term tactics and long-term strategy, principles he would apply rigorously in his pursuit of the mysteries of protein folding and function. Like many of his generation, Dr. Fersht entered science because of his curiosity and he has always been drawn to novel areas: “if I saw a crowd running in one direction, I would walk slowly in the opposite.” As an undergraduate at the Cambridge University, he pursued his interests in chemistry, with a focus on physical chemistry. In his PhD work at Cambridge (completed in 2 years, 8 months!), he became—under the benign neglect of his supervisor, Anthony Kirby—a self-taught kineticist and experimentalist. After a postdoctoral stint with Bill Jencks at Brandeis, where he learned the art of rapid-mixing experiments, he returned to Cambridge to the MRC Laboratory of Molecular Biology as a group leader apply his skills as a mechanistic chemist in the new area of structural biology. In 1978 Dr. Fersht became Professor of Biological Chemistry at London University (Imperial College). In 1988 he returned to Cambridge as Herchel Smith Professor of organic Chemistry, where he headed the MRC Unit for Protein Function and Design until 2010. Dr. Fersht currently serves as group leader at the Laboratory of Molecular Biology.

Dr. Fersht is perhaps best known for developing protein engineering as a potent tool to investigate mechanisms of enzyme catalysis and protein folding. Site-directed mutagenesis using synthetic DNA was demonstrated in 1978, but the technique languished because there were precious few ideas of what to do with it. Dr. Fersht realized that it was the precise tool he needed to determine how noncovalent interactions between amino acid side chains mediated specificity of binding, enzymatic catalysis, and protein folding. By introducing different amino acids at specific sites, he could, in essence, make small changes in the side chains, allowing him to probe interactions between the enzyme and substrate, which he first demonstrated by altering the specificity of tyrosyl-tRNA synthetase. Over the next 10 years, Dr. Fersht exploited this technological and intellectual advantage, publishing 16 *Nature* papers, without a single rejection. In short, he revolutionized the study of protein structure, enzyme mechanism, and protein folding.

No discussion of Dr. Fersht can be complete without mention of his seminal textbook: *Enzyme Structure and Mechanism.* When his invited review for *Annual Reviews of Biochemistry* was rejected by the senior editor, he expanded it into a textbook that has become a standard in the field. A Fellow of the Royal Society, Dr. Fersht has received numerous honors and awards, was elected as a foreign member of the National Academy of Sciences, and has co-founded three biotech companies. In 2003 he received a knighthood from Her Majesty Queen Elizabeth.

Dr. Roger Y. Tsien infused a rainbow of colors into the biological sciences, revolutionizing cell biology by allowing scientists to peer inside living cells and watch the behavior of molecules in real time. A 34th-generation descendant of the royal family of the Kingdom of Wuyue, Dr. Tsien was born in New York City, the third son of parents who had emigrated from China. His brother, Richard, a prominent scientist at Stanford, now admits to giving Dr. Tsien his American first name in honor of the famous cowboy actor, Roy Rogers. As a young boy, Dr. Tsien became fascinated with chemistry by following experiments from a library chemistry book—his parents had given him a Gilbert Chemistry Set, but the experiments were too tame. He particularly remembers growing striking magenta, blue, and green crystals of metal salts in silica gardens, and watching the oxidation of MnO$_4^-$ (intense purple) to MnO$_4^{2-}$ (beautiful green). These experiments “reflect an early and long-lasting obsession with pretty colors.” His first research experience was as part of an NSF-sponsored summer program at Ohio University; he later entered his project in the Westinghouse (now Intel) Science Talent Search, and won

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Dr. Roger Y. Tsien (concluded)

the nationwide science fair competition. In 1968 he entered Harvard to become a chemist, but was diverted to neurobiology by exposure to a course run by the charismatic duo of David Hubel and Torsten Wiesel—future Nobel laureates—who shamelessly proselytized undergrads to become neuroscientists. In 1972 Dr. Tsien pursued PhD studies in neurobiology at Cambridge, UK where he focused on synthesizing dyes for Ca^{2+} imaging. After a postdoctoral stay at Cambridge, he sought a faculty position, but had a surprisingly hard time as a chemical biologist, long before it became fashionable. He initially joined the faculty at University of California, Berkeley, but in 1989 moved to the Department of Chemistry and Biochemistry at UC, San Diego, where he is now Professor and an Investigator of the Howard Hughes Medical Institute.

Early in his graduate career, Dr. Tsien realized that he did not enjoy the standard electrophysiological approach of dropping microelectrodes into brains and recording hundreds of response from individual neurons: he wanted to “see” the changes in a neuron when it fired an action potential, but there were no suitably sensitive dyes available. His first success at synthesizing such a dye was BAPTA, a modified version of EGTA that responded optically to Ca^{2+} binding. At Berkeley, he generated improved Ca^{2+} and Na^{+} indicators, but a collaborative project with Susan Taylor made it clear that a new approach was needed. He had attached rhodamine to the regulatory subunit of protein kinase A and fluorescein to the catalytic subunit, in order to study their dissociation, using FRET. Although informative, the whole chemical process was extremely tedious and the proteins then had to be injected into cells. It was at this point that he came across a recent paper describing the cloning of the green-fluorescent protein...and realized its potential. He quickly showed that GFP formed its light-sensitive chromophore spontaneously in the presence of oxygen, modified GFP to enhance its spectral characteristics to make it more useful, and changed the amino acids around the chromophore to generate FPs that fluoresced at different wavelengths, ultimately generating a rainbow of fluorescent proteins that have transformed our study of biology.

Dr. Tsien has received numerous honors and awards, including election to the National Academy of Sciences in 1998. In 2008, he was awarded the Nobel Prize in Chemistry, which was shared with Martin Chalfie and Osamu Shimomura, for “GFP: discovery, expression, and development.”