

Garland R. Marshall, Ph.D.

Garland R. Marshall is currently Professor of Biochemistry and Molecular Biophysics and of Biomedical Engineering and a member of the Center for Computational Biology at Washington University Medical School in St. Louis, Missouri. He graduated from the California Institute of Technology with a B.S. in biology in 1962. He received his Ph.D. in 1966 from the Rockefeller University and was immediately recruited to a faculty position at Washington University Medical School where he has remained, rising to Professorial rank in 1976.

Prof. Marshall has been a significant factor in the development of two important technologies that have revolutionized the practice of biological sciences. First was the development of solid-phase synthesis starting as the first graduate student in the laboratory of R. Bruce Merrifield, Nobel Laureate, during the initial development of peptide synthesis using a polymeric support. The success of this approach in the synthesis of peptides and now the routine synthesis of small proteins has led to its adoption for the synthesis of biopolymers (nucleic acids and oligosaccharides) as well as its adoption recently by the synthetic organic community as the basis for combinatorial chemistry, the innovation in drug discovery of the nineties.

His second scientific area of significant impact was the development of molecular modeling and associated computer graphics approaches to three-dimensional structure-activity studies and the design of novel therapeutics. In 1967 at Washington University, a molecular modeling system was developed on a LINC computer (2K memory 12-bit word, oscilloscope output with real-time rotation of small molecules and an input string similar to SMILES). This system was immediately used to explore the conformational impact of methyl for proton substitution on peptide backbones, and led to the discovery of the dramatic impact of replacing the α -proton with a methyl group in forcing a helical conformation on the peptide backbone. Further efforts in computer graphics led to exploration of computer architectures for molecular modeling with modular computer components (macromodules), and the first hardware (MMS-X hardware/software system distributed to many crystallography labs) designed for electron density fitting in building molecular models from X-ray data. Marshall and his colleagues developed algorithms that allowed analysis of three-dimensional structures of sets of molecules active at the same receptor (Active Analog Approach and subsequently Active Site Mapping). From these analyses, predictive models were obtained which could be used to guide the synthesis of novel compounds as potential new drugs. In 1979, Marshall founded a company, Tripos (Nasdaq, TRPS), that further developed and marketed hardware/software in this area. The software SYBYL



originally derived from the Marshall group at Washington University is currently in use in essentially every major pharmaceutical company.

Marshall believes that computational results require experimental validation. Marshall first described a peptide inhibitor of the angiotensin II, a hormone involved in hypertension. He has led the exploration of peptidomimetics in which chemical constraints are used to determine the receptor-bound conformation of biologically active peptides. The ability of peptidomimetics to mimic reverse turns and nucleate β -sheet hairpins has been explored both computationally and experimentally. Marshall pioneered the development of HIV protease inhibitors for the treatment of AIDS; the first crystal structure of HIV protease complexed with an inhibitor utilized the inhibitor MVT-101 from the Marshall lab. Most recently, Marshall has experimentally determined the conformation of a peptide ligand when bound to a G-protein coupled receptor. Exploration of the molecular interaction between rhodopsin and its G-protein, transducin, and the mechanism of signal transduction is a current focus of his research. In the last few years, modeling of metals in biological systems has become a research objective. Prof. Marshall founded Metaphore Pharmaceuticals in 1995 to develop novel ligands for metals through combinatorial chemistry for therapeutic applications. An enzyme mimetic of superoxide dismutase developed by Metaphore has completed Phase II clinical trials.

In 1988, Marshall received the Medicinal Chemistry Award from the Medicinal Chemistry Division of the American Chemical Society. Prof. Marshall was awarded an honorary degree (D.Sc.) in 1994 by the Polytechnika (Technical University) in Lodz, Poland. This degree recognizes Prof. Marshall's contributions to the field of peptide chemistry and to the application of computational chemistry to determine the biologically relevant conformation of peptides. He received the Vincent duVigneaud Award administered by the American Peptide Society the same year.

Marshall received the 1996 Regional Commerce and Growth Association Science and Technology Award in recognition of the impact of his scientific contributions to the St. Louis area. In addition, he also received the Midwest Award from the St. Louis section of the American Chemical Society given to a scientist for meritorious contributions to chemistry from the seven-state mid-west region. In July of 2000, he received the Cathay Award from the Chinese Peptide Society. In 2000, he also received the Taito M. Soine Memorial Award from the Department of Medicinal Chemistry at the University of Minnesota in "recognition of his outstanding contributions to the field of medicinal chemistry". Prof. Marshall was the recipient of the Merrifield Award from the American Peptide Society presented at the International Peptide Symposium in San Diego in June, 2001. In 2003 he received an Excellence in Life Sciences Entrepreneurship Award from the Missouri Biotechnology Association.

Prof. Marshall also serves on the SAB of the Institute for Molecular Biosciences, University of Queensland, Brisbane, Australia, the SAB of MDS Capital of Toronto, Canada, the Board of Directors of Metaphore Pharmaceuticals as well as a Trustee for the Torrey Pines Institute for Molecular Sciences in La Jolla, California.