Ralph F. Hirschmann (1922–2009)

Ralph Franz Hirschmann, one of the great pioneers in peptide chemistry and an internationally respected scientist in medicinal chemistry, died on June 20, 2009 at his home in Lansdale, Pennsylvania at the age of 87. Trained as an organic chemist in the synthesis of steroids, he matured into a world-class scientist who made seminal contributions to peptide chemistry, protein chemistry, and medicinal chemistry with profound impact in biomedical sciences both at the academic and industrial levels. With a deep understanding of mechanistic and structural biochemistry, he successfully pioneered the interdisciplinary field of chemical biology by integrating chemistry and biology concepts to produce research achievements not attainable by either discipline alone.

Hirschmann was born on May 6, 1922 in Fürth (Bavaria), Germany. He attended the *Gymnasium* in Fürth until December 1936, when the Hirschmann family fled Germany for the United States and settled in Kansas City. After graduating from Oberlin College in 1943, he served three years in the U.S. Army in the Pacific. He later returned to complete his doctorate in organic chemistry at the University of Wisconsin in 1950 under the guidance of William S. Johnson, and was subsequently recruited as a researcher at Merck laboratories (Rahway, USA).

In his early career as a steroid chemist, he used steroidal *N*-acetylglucosamides to successfully direct the release of active steroid at the site of inflammation. Hirschmann coined this process "drug latentiation" long before the concepts "prodrugs" and "targeted drug release" were widely applied by others to improve the therapeutic index of a biologically active compound.[1]

In the 1960s, together with Robert G. Denkewalter, he began working in peptide chemistry. Through his reinstitution of the use of *N*-carboxyanhydrides, both to protect and activate amino acids he was able to achieve a controlled synthesis of peptides. Additionally, with the discovery of a number of amino acid protecting groups, most notably of the S-acetamidomethyl group for cysteine residues, he led Merck's peptide group to complete the first total synthesis of the enzyme ribonuclease S in solution[2a] concurrently with Merrifield's solid-phase synthesis of ribonuclease A.[2b] These chemical syntheses of active enzymes were achieved at a time when it was widely believed that a chemical synthesis of a protein without the use of a template was impossible. As a result of these two syntheses, Anfinsen's principle that the correct folding of a protein is uniquely determined by the amino acid sequence and is independent of the living system was unequivocally confirmed.[3a,b]

With increasing responsibility in research management at Merck, Ralph Hirschmann was promoted to Senior Vice President of Basic Research in 1978, and in 1984 to Senior Vice President of Chemistry. It was at this time that he began to explore the potential of cyclic peptides as medicinal agents by applying the above concept for example to renin inhibitors and subsequently to the design of protease-resistant somatostatin analogues of high potency.[4]

Because of his strong commitment to science, it was easy for Hirschmann to make the transition into the academic environment after his obligatory retirement from Merck in 1987. He was invited to join the faculty of the University of Pennsylvania, where he served as the Rao Makineni Professor of Bioorganic Chemistry until 2006. In very successful collaborative research with Amos B. Smith and K. C. Nicolaou, nonpeptidic scaffolds were developed to display pharmacophoric amino acid side chains in peptidomimetic mode as receptor ligands or enzyme inhibitors.[5] Furthermore, a collaboration with Stephen Benkovic at Pennsylvania State University investigating catalytic antibodies led to the discovery of a monoclonal antibody capable of catalyzing the coupling of amino acids and peptides. This discovery demonstrated the potential of such novel approach for catalyzing the ligation of large unprotected protein fragments.[6]

Along with the numerous awards Ralph Hirschmann received from the American Chemical Society, his scientific work has been recognized with the Alan E. Pierce Award (renamed the Bruce Merrifield Award) from the American Peptide Society (1983), the Max Bergmann Medal of the Max Bergmann Kreis (1993), and the Josef Rudinger Award of the European Peptide Society (1996). Furthermore, he was presented with the National Medal of Science by President Clinton in 2000.

In 1989, Merck Sharp & Dohme established the ACS "Ralph F. Hirschmann Award in Peptide Chemistry" in recognition of his outstanding achievements in this research field. With this lasting tribute to the great scientist, he will be remembered not only by the many colleagues and friends in both industry and academia, but his legacy will always be remembered even by the younger generation of peptide and medicinal chemists.

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