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Stephen B. H. Kent (December 12, 1945 in Wellington, New Zealand) is a chemistry professor at the University of Chicago

Biography

Dr. Kent received his Chemistry Ph.D. from the University of California, Berkeley in 1975, his M.Sc. from Massey University, Palmerston North, New Zealand in 1970, and his B.Sc. degree in 1968 from Victoria University of Wellington, New Zealand.

Following his post-doctoral work in the laboratory of Robert Bruce Merrifield at the Rockefeller University, Dr. Kent continued research there as an assistant professor through 1981. He has also held faculty positions at the California Institute of Technology, Bond University in Australia, and the Scripps Research Institute in California. Currently Dr. Kent is a Professor in the Departments of Biochemistry & Molecular Biology, and Professor of Chemistry at the University of Chicago. From 2003-2009 he also served as the Director of the Institute for Biophysical Dynamics. In addition to his academic achievements, in the 1990s he was the founder of two San Francisco Bay Area companies: CIPHERGEN Biosystems and Gryphon Sciences.

Dr. Kent has received international recognition for his research achievements. In 1994 he received the Ralph F. Hirschmann Award in Peptide Chemistry from the American Chemical Society, the inaugural Kaiser Award from the Protein Society in 2002, the du Vigneaud Award from the American Peptide Society (2004), the 2009 Merrifield award from the American Peptide Society, the Rudinger Medal from the European Peptide Society (2010), the Akabori Medal from the Japanese Peptide Society (2010), the Alfred Bader Award in Bioorganic Chemistry (2011) from the American Chemical Society, the Leach Medal from the Lorne Protein Conference (2013), the Prelog Medal for stereochemistry from the ETH Zurich (2017), and the inaugural Ernesto Scoffone Award from the Italian Peptide Society (2018). Dr. Kent is an Honorary Fellow of the Royal Society of New Zealand. He was elected Fellow of the American Association for the Advancement of Science in 2000, and Fellow of the Royal Society of Chemistry in 2008.

In May 2016 *Journal of Peptide Science*, edited by Luis Moroder, published a Festschrift in celebration of his 70th birthday.

Research Interests:

Prof. Kent's research is focused on understanding the molecular basis of protein function, particularly the physical organic chemistry of enzyme catalysis. To that end, his group develop novel methods for the total synthesis of proteins that enable them to apply advanced physical methods in unprecedented ways to understand the chemical origins of protein structure and function. They then demonstrate that knowledge by the design and construction of protein molecules with novel properties.

Chemical Protein Synthesis

The Kent research group pioneered the effective total chemical synthesis of protein molecules. The long polypeptide chain of the protein molecule is prepared in a convergent fashion by 'chemical ligation', the chemoselective condensation of unprotected peptide segments that contain unique, mutually reactive functional groups. They developed the most powerful ligation chemistry – thioester-mediated, amide-forming ligation at Xaa-Cys sites, termed 'native chemical ligation'. The resulting polypeptide chains are then folded with great efficiency to give high purity synthetic proteins. The covalent structure of the synthetic protein is confirmed by mass spectrometry, and its three dimensional folded structure is determined by high resolution X-ray crystallography. Synthetic



proteins have full biochemical and biological activities. Chemical protein synthesis is generally applicable to the efficient preparation of protein molecules > 30 kDa, with polypeptide chains containing 300 or more amino acids.

Total synthesis enables the versatile incorporation of non-coded amino acids into proteins, and the modification and labeling of protein molecules without restriction as to the sites, numbers, and kinds of chemical moieties being introduced.

Racemic Protein Crystallography and Mirror Image Drug Discovery

Total chemical synthesis enables us to make mirror image 'D-protein' molecules not found in Nature. The Kent group has pioneered the use of racemic & *quasi-racemic* protein crystallography to determine the X-ray structures of proteins that otherwise will not crystallize, and to obtain protein electron density maps of unprecedented quality.

In collaboration with Sachdev Sidhu (Toronto) they prototyped the use of mirror image protein targets prepared by total chemical synthesis, to identify novel protein molecule binders from phage-displayed libraries. Synthesis of the enantiomer of the identified protein binders gives unique D-protein molecules, which could not have been discovered using the natural target. These synthetic D-proteins are effective against the natural target protein, and have the specificity and potency of antibodies. D-Proteins are non-immunogenic, non-toxic, resistant to natural proteases, long-lived in vivo, and show great promise as candidate human therapeutics.

Education & Past Positions

Victoria University of Wellington, B.Sc., 1968

Massey University, M.Sc., 1970

University of California, Berkeley, Ph.D., 1975

The Rockefeller University, Research Associate, 1974-1977; Assistant Professor, 1977-1981

California Institute of Technology, Senior Research Associate, 1983-1989.

Bond University, Professor, 1989-1990

The Scripps Research Institute, Member & Professor, 1991-1996

Gryphon Sciences, Chief Scientist, 1997-2000

The University of Chicago, Professor, 2001-

Director, Institute for Biophysical Dynamics, 2003-2009

Joint appointment with the Department of Biochemistry & Molecular Biology

Awards

Inaugural Ernesto Scoffone Award, Italian Peptide Society 2018

Prelog Medal 2017

Leach Medal, Lorne Conference on Protein Structure & Function 2013

Bader National Award in Bioorganic Chemistry, American Chemical Society 2011



Akabori Medal, Japanese Peptide Society 2010
Rudinger Medal, European Peptide Society 2010
R. Bruce Merrifield Award, American Peptide Society 2009
Vincent duVigneaud Award, American Peptide Society 2004
E.T. Kaiser Jr. Award for Innovation in Protein Science, The Protein Society 2002
Hirschmann National Award in Peptide Chemistry, American Chemical Society 1994

Selected Publications

P. P. Dawson, T. W. Muir, I. Clark-Lewis, S. B.H. Kent Synthesis of proteins by native chemical ligation
Science, 1994

Canne, L. E., Bark, S. J., Kent, S. B. H. Extending the applicability of native chemical ligation *Journal of the American Chemical Society* 1996

Paul S Marinec, Kyle E Landgraf, Maruti Uppalapati, Gang Chen, Daniel Xie, Qiyang Jiang, Yanlong Zhao, Annalise Petriello, Kurt Deshayes, Stephen BH Kent, Dana Ault-Riche, Sachdev S Sidhu A Non-immunogenic Bivalent d-Protein Potently Inhibits Retinal Vascularization and Tumor Growth *ACS Chemical Biology* **2021**

Vladimir Torbeev, Stephen BH Kent Chemical Synthesis of an Enzyme Containing an Artificial Catalytic Apparatus *Australian Journal of Chemistry* **2020**

Kent SBH, Novel protein science enabled by total chemical synthesis, *Protein Science*, **2019**

Kent SBH, Racemic & quasi-racemic protein crystallography enabled by chemical protein synthesis, *Current Opinion in Chemical Biology*, **2018**

Bobo Dang, Tomoya Kubota, Rong Shen, Kalyaneswar Mandal, Francisco Bezanilla*, Benoit Roux*, Stephen B. H. Kent*, Inversion of Thr and Ile side chain stereochemistry in a protein molecule: impact on the folding, stability, and structure of the ShK toxin protein molecule, *Angewandte Chemie Int. Ed.*, **2017**

Gates ZP, Baxa MC, Yu WY, Riback JA, Li H, Roux B, Kent SBH, Sosnick TR, The perplexing cooperative folding and stability of a low sequence complexity, poly-proline 2 protein lacking a hydrophobic core, *Proc. Nat. Acad. Sci. USA*, Feb. 13, **2017**

David J. Boerema, Valentina A. Tereshko, JunLiang Zhang, Stephen B. H. Kent, Chemical synthesis and enzymatic properties of RNase A analogues designed to enhance second-step catalytic activity, *Org. Biomol. Chem*, **2016**

Bobo Dang, Tomoya Kubota, Kalyaneswar Mandal, Ana M. Correa*, Francisco Bezanilla*, Stephen B. H. Kent*, Elucidation of the covalent and tertiary structures of biologically active Ts3 toxin, *Angewandte Chemie Int. Ed.*, **2016**,

Maruti Uppalapati, Dong Jun Lee, Kalyaneswar Mandal, Hongyan Li, Les P. Miranda, Joshua Lowitz, John Kenney, Jarrett J. Adams, Dana Ault-Riché, Stephen B. H. Kent, Sachdev S. Sidhu, A potent D-protein antagonist of VEGF-A is non-immunogenic, metabolically stable and longer-circulating in vivo, *ACS Chemical Biology*, **2016**



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K. Mandal, B. Dhayalan, M. Avital-Shmilovici, A. Tokmakoff, S.B.H. Kent, Spontaneous resolution of crystalline insulins from quasi-racemic solutions: Xray structure determination of isotope-labeled ester-insulin and human insulin, ChemBioChem, **2016**

B. Dhayalan, A. Fitzpatrick, K. Mandal, J. Whittaker, M. A. Weiss, A. Tokmakoff*, S. B. H. Kent*, Efficient total chemical synthesis of $^{13}\text{C}=^{18}\text{O}$ isotopomers of human insulin for isotope-edited FTIR, ChemBioChem, **2016**

Richard D. Bunker, Kalyaneswar Mandal, Ghader Bashiri, Jessica J. Chaston, Brad Pentelute, J. Shaun Lott, Stephen B. H. Kent*, Edward N. Baker*, A functional role of Rv1738 in Mycobacterium tuberculosis persistence suggested by racemic protein crystallography., Proc. Natl. Acad. Sci. USA, March 23, **2015**