UCSD Pharmacologists Collaborate On New Approach To Drug Design

March 22, 2004

Sue Pondrom

French and American researchers have developed a unique approach to drug design where an important neuron-signaling enzyme called acetylcholinesterase (AChE) acts as a microscopic vessel filled with reactant chemicals, to create its own, tailored therapeutic agent.

While current AChE inhibitors are widely used to treat neuromuscular and cognitive disorders, the new process offers the potential for development of more potent drugs with fewer side effects.

Published in a recent issue of *Proceedings of the National Academy of Sciences (PNAS)* (February 10, 2004), the study described how the AChE molecule, serving as a surface, or template for the reactions, brings the reactant components into proximity to form an inhibitor of the enzyme that is both potent and highly specific for the enzyme.

The investigators from the French National Center for Scientific Research, the University of California, San Diego (UCSD) and The Scripps Research Institute (TSRI), noted that the formation of the inhibitor on the enzyme template proceeds about a million times more rapidly than under typical laboratory conditions in test tubes.

"The enzyme template is a fluctuating structure with many inherent conformations," said one of the study's authors, Palmer Taylor, Ph.D., dean of the UCSD School of Pharmacy and Pharmaceutical Sciences. "The imaginative synthetic 'click chemistry' developed by the TSRI group headed by K. Barry Sharpless, freezes 'in-frame,' like a single frame of a motion picture, the conformation selective for the inhibitor."

He added that "while the compounds formed by click chemistry have high affinity for their targets, the real potential lies in the selectivity of the inhibitor formed on the target surface for one of the many closely related enzymes or drug receptors."

The study was led by structural biochemists, Drs. Pascale Marchot and Yves Bourne, currently with the French National Center for Scientific Research in Marseille, France, and formerly visiting faculty at the UCSD School of Medicine and TSRI. A key role in the research was played by Taylor, also a UCSD professor of pharmacology, and project scientist Zoran Radic, Ph.D. The UCSD team characterized the binding sites, the conformation and the structural fluctuations in AChE, and the molecular template on which the chemical reactions occurred.

Click chemistry, that facilities specific chemical reactions on an enzyme or drug target surface, is a process developed three years ago by Sharpless, who, with colleague Hartmuth Kolb, Ph.D., participated in the research by characterizing the detailed reaction mechanism and product formed from a combination of reactants.

The work was supported by grants from the Association Francaise contre les Myopathies, the U.S. Public Health Service, the Department of Army Medical Defense, the National Institutes of Health, the National Science Foundation, and the W.M. Keck Foundation.

Contact: Sue Pondrom (619) 543-6163