PROTEIN STRUCTURE SIMILARITY CLUSTERING (PSSC) AS GUIDING PRINCIPLE FOR CHEMICAL GENOMICS

Herbert Waldmann

Max-Planck-Institut für molekulare Physiologie, Department of Chemical Biology, Otto-Hahn-Str. 11, D-44227 Dortmund, and Universität Dortmund, Fachbereich 3, Organische Chemie, D-44221 Dortmund, Germany.
Herbert.waldmann@mpi-dortmund.mpg.de

In the everlasting effort to find small molecules which alter protein function and ultimately might lead to new drugs, combinatorial chemistry has emerged as a very powerful tool. Opposite to the original thought that large library sizes will result in the discovery of many hit and lead structures, it has been recognized that biological relevance, design, and diversity of the library are more important. As the universe of thinkable compounds is almost infinite, the question arises: Where is a biologically validated starting point to build a combinatorial library around? Nature itself might give an answer: Natural products have been evolved to bind to proteins. Recent results in structural biology and bioinformatics indicate that the number of distinct protein families and folds is fairly limited. Often the same structural domain is used by many proteins in a more or less modified form created by divergent evolution. This structural conservatism of Nature can be exploited for the design of biologically relevant molecules derived from natural products addressing the ligand-sensing cores of these domains. In the lecture arguments for a natural product guided library design will be discussed and highlighted by its recent application in the synthesis of combinatorial libraries of biologically active compounds.[1)]

1) R. Breinbauer, I. R. Vetter, H. Waldmann Angew. Chem. Int. Ed. **2002** *41*, 2878-2890.
2) M. A. Koch, L.-O.Wittenberg, S. Basu, D. A. Jeyaraj, E. Gourzoulidou, K. Reinecke, A. Odermatt, H. Waldmann, Proc. Natl. Ac. Sci, **2004**, *101*, 16721-16726.