

W0053

Structural Genomics and Structure- based Rational Drug - Design against Inflammation, Rheumatism and Arthritis. S. Dey, R.K. Somvanshi, V.K. Goel, P. Ramakrishnan, S. Mittal, N. Singh, A.S. Ethayathulla, S. Sharma, T.P. Singh, Dept. of Biophysics, All India Inst. of Medical Sciences, New Delhi-110029.

One of the most important goals in modern structural biology is to design and be able to produce in sufficient quantity, drugs that will act in a specific way with minimal side effects. Traditionally, scientists identify new drugs either by fiddling with existing drugs or by testing thousands of compounds in a laboratory. This approach is lengthy, tedious, time consuming, expensive and still uncertain. Therefore, a more rational strategy is needed to be adopted. Structure- based approach promises to eliminate various loopholes of existing methods of new drug discovery. In this effort, the first step is to identify the details of its binding site. As a second step, using the details of the binding studies are done to determine its efficacy in the laboratory set ups. The designed compounds that show affinities in the acceptable pharmacological range are taken further for other biological assays and clinical trials. We report here the efforts of our group in developing specific substances against rheumatism, arthritis and inflammation using structure- based drug design approach. In this study, phospholipase A₂ (PLA₂) and cyclooxygenases COX1 / COX 2 were used as targets and peptides were designed as ligands. The structures of a number of PLA₂s and their complexes with natural and designed ligands have been determined in our lab and molecules showing inhibitions at picomolar concentrations have been obtained. Similarly, based on the detailed structural information of the binding sites of COX1 and COX2, we have designed a number of ligands against both COX1 and COX2. We have already obtained clear leads and further studies to improve their efficacies are in progress.