Protein Structures as Templates for the Design of New Drugs

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Einleitung

Die internationale Tagung vom 22. November 1996, organisiert von der Sektion Chemische Forschung der Neuen Schweizerischen Chemischen Gesellschaft, gab einen Überblick über das Gebiet der Proteine. Die Forscher können den räumlichen Aufbau der Proteine immer genauer ermitteln und in dreidimensionalen Darstellungen zeigen. Computerprogramme ermöglichen es Pharmakologen und medizinalen Chemikern, die Lage von Wirksubstanzen auf ihren Rezeptoren gezielter zu zeigen, sie masszuschneidern und ihre Eigenschaften zu verstehen. Die Technik wurde am Beispiel von Protein-Enzymen entwickelt und für die Schaffung von Enzym-Inhibitoren verfeinert.

Es gibt noch eine Vielzahl von Proteinen, die mindestens ebenso interessant und wichtig sind wie Enzyme. Gewisse Proteine machen Kontakte mit anderen Proteinen, um einer Zelle ein pharmakologisches Signal zu geben. Werden Struktur und Funktion von solchen Signal-Biomolekülen, wie Enzymen, mit Hilfe von kernmagnetischen Resonanzen in physiologischer Lösung und mit Hilfe von computergestützten Methoden untersucht, wird sich ein neuer Weg zu effizienten Medikamenten eröffnen.

Das Ziel dieser Tagung war, dieses Forschungsgebiet bekannt zu machen und ihm neue Impulse zu vermitteln. Zusammenfassungen der Vorträge dieser Protein-Tagung sollen den gleichen Zweck erreichen. Die Vorträge wurden entweder von den Autoren selbst oder von Spezialisten zusammengefasst.

R. Wenger, Chairman der Tagung

Ligand Discovery Using Three-Dimensional Structures [1]

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There are now over 4000 protein structures deposited in the Brookhaven Data Base which have been determined by protein X-ray crystallography or NMR spectroscopy. This still falls quite some way short of providing a structural model for each of the 100 000 or so gene products of the human genome. The rapidly expanding sequence and structure catalogue of these proteins is, however, already helping to answer many complex questions about signal transduction and cell-cell recognition. Of immediate pharmaceutical

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interest is how to use this structural information to discover new ligands. The various approaches can be classified in three general ways. 1) Template Mimicry: a number of proteins are ligands in their own right and copies of small loops or fragments from the parent protein may provide biological activity. 2) Lead optimization: in this approach, a known substrate or inhibitor is modified to enhance binding and inhibitory properties based on the 3D template structure of the protein. There are now over ten examples of this approach having been used to successfully design clinically tested drugs which include inhibitors for HIV protease, neuraminidase and thymidylate synthase. 3) Ab initio design and database mining provide the third general approach which

is being advanced by computer programs which fit molecules or molecular fragments into a defined protein template. This can involve for searching very large 3D databases of available or synthetically tractable molecules or the design of new molecules.

The immunoglobulin domain family of proteins including adhesion molecules provide examples of the possible application of template mimicry in ligand design. The vascular cell adhesion molecule (VCAM) consists of a linear array of seven immunoglobulin domains stretching out over 20 nm into the extracellular space to recognize and recruit passing leukocyte cells. Mutation studies show that six or seven residues (T37QIDSPL) at the tip of a loop region are the key to the recognition and binding. We have recently solved a new crystal form of the D1,D2 domains of VCAM which shows a conserved conformation of this exposed recognition loop when compared with the two other available X-ray structures of these domains [2][3]. An analogue cyclic hexapeptide of this loop (CQIDSPC) has been shown to inhibit VCAM binding to the integrin receptor [2]. The approach of making cyclic peptide mimics is particularly well suited to Ig folds as the recognition region normally consists of a peptide loop.