Acta Cryst. (1995). D**51**, 405–406

Preface

The Structure-Based Drug Design Conference, held at Edgewater Beach Resort, Panama City Beach, Florida, April 22–25, 1994, was concerned with the use of structural analyses of complexes of drugs and their target proteins so that new drugs with a higher medical efficacy can be designed. The major thrust of this conference was the use of three-dimensional data obtained by the methods of X-ray diffraction of crystalline materials for analyses relevant to drug design. The many types of information that are required for such structure-based drug design were described by scientists from industry and from academia, so that this conference provided a significant merging of scientific expertise.

Progress in drug design has accelerated in recent years as a deeper understanding of the required structural principles has been obtained. Details of the methods used in structure-based drug design were described and evaluated during the course of the conference so that aspects that are potentially scientifically productive and those that need more investigation were revealed. Many examples of the use of computational methods were provided, and the importance of computational literacy in terms of representations and of database availability was stressed.

Many elegant uses of macromolecular crystallography in drug design were described in presentations that were focused on relevant structural results. Such analyses have led to drug candidates in all phases of clinical development, as well as one approved drug, a topical carbonic anhydrase inhibitor. The need to consider drug-development issues such as bioavailability, toxicity, side effects and resistance in the design process was recognized and applications of structure-based methods to some of these problems were discussed.

The results of high-resolution crystal structure analyses provide information that is invaluable for modeling drug–receptor binding. Intermolecular interactions around functional groups in crystals give information on directional preferences of binding that can be used to develop better force fields for drug design. Rules can be generated such as, for example, that metal ions generally bind in the planes of carboxyl groups or histidine rings, and that, although each is weak, C—H···O and C—F···H—C interactions can help align molecules in a hydrophobic environment. Zinc, chosen for analysis in a review here, is important for binding and catalytic activation of substrates in enzymes, as well as for stabilization of any tetrahedral reaction intermediates. Therefore, ligand and geometrical preferences of zinc in an unstrained system were analyzed. The possibility of searching a computational library of known crystal structures for substructures of similar geometry is provided by programs such as *LORE*, a protein database management tool. A practical example is given here of three-dimensional quantitative structure–activity results in which *GRID* force field and *GOLPE* variable selection are used for an analysis of the binding of glucose analogues to the enzyme glycogen phosphorylase.

The structure-aided design of antiviral agents, which lead to inferences on the mode of activity of each drug is described in several articles. The antiviral drug WIN51711 has been shown to bind to the Sabin strain of type 3 poliovirus, and the structure of the complex has been determined at 2.9 Å resolution. WIN drugs inhibit the uncoating of virus during infection by stabilizing the capsid against any receptor-induced conformational change. This binding of WIN drugs to poliovirus has been compared with their binding to rhinovirus 14. The drug works in a different way, but effectively, against both viruses. For example, in human rhinovirus serotype 14 (HRV14) large conformational changes are observed in coat protein after binding, while no such change is found to occur with poliovirus. Four methyltetrazole-containing antiviral groups bound to HRV14 have been studied at 2.9 Å resolution. They bind in the VP1 hydrophobic pocket, but at a somewhat different site from that to which WIN compounds bind. The resulting effects of the drug binding has been addressed by studies of the manner in which WIN51711-resistant mutants of poliovirus type 3 bind to capsid-binding drugs. Amino-acid substitutions in these mutants that permit the virus to produce progeny in the presence of the drug are generally in the area of the viral canyon base, the lining of the drug-binding pocket, and the base of the protomer. These are identified as the sites for the transmission of the uncoating signal from the receptor. In other structure–activity studies, benzoic acid inhibitors of influenza virus neuraminidase have been investigated by iterative cycles of modeling, synthesis, biological testing and X-ray diffraction.

Immune system applications of structure-aided drug design are covered in several articles. The nature of organ transplant rejection is being revealed by this work. The X-ray crystal structure of the major binding protein for the immunosuppressant FK506 (tacrolimus) has been determined in an unliganded form and in complex with FK506 and rapamycin. FK506 is a natural product used successfully in organ transplantation. Its 12 kDa cytosolic receptor is FKBP12. The FK506 complex with FKBP12 is a potent agonist of immunosuppression and appears to act by inhibition of the phosphatase activity of calcineurin. Rapamycin (sirolimus) (which is itself an immunosuppressant by a different mechanism) competes with FK506 for binding to FKBP12 and thereby acts as antagonist of calcineurin inhibition. The crystal structures of 16 ligand com-

ISSN 0907-4449

plexes of FKBP12 show structural variability, suggesting that immunosuppressive ligands express their differential effects in part by modulating the conformation of FKBP12 and not simply through differences in the ligand structures themselves. The crystal structures of protein bound macrocyclic inhibitors of FKBP12 that are comparable in binding, potency and peptidyl prolyl isomerase inhibition, which are not immunosuppressive are reported. The calcium-dependent calcineurin, when inhibited by the FKBP12–FK506 complex, interrupts the T-cell activation events leading to immunosuppression. The compounds here may adversely affect binding of calcineurin. Another enzyme that may be inhibited in order to prevent the rejection of transplanted organs is purine nucleoside phosphorylase (PNP). PNP converts purine nucleosides and phosphate into purine bases and sugar phosphate. Inhibitors of PNP block proliferation of T cells and appear promising for treating T-cell mediated autoimmune diseases, including arthritis and psoriasis. X-ray analyses of highly potent inhibitors and the experimentally determined binding energies are compared with calculated values by use of *X-PLOR*, *DelPhi* and *SoftDock*. The use of molecular dynamics for structure-based drug design is described for the example of the binding of a non-natural nonapepitide to the class I major histocompatibility complex.

Several other studies of medical significance are reported here. One involves studies of blood clotting agents. The crystal structures of two active-site mimetic inhibitors bound to human thrombin are described. One inhibitor approximates a turn found in the conformation of fibrinopeptide A which is normally catalytically released by thrombin in the activation of fibrinogen. The second inhibitor binds in a manner that is a cross between that of a normal substrate and the abnormal binding of hirudin, a potent natural inhibitor isolated from leeches. The program *CHARMm* was used to give intermolecular interaction energies after energy minimization of modeled complexes using various dielectric functions.

The enzyme trypanothione reductase from *Crithidia fasciculata* (a parasite) is a target for structure-aided drug design of antiparasitic drugs. Two independent studies show where there is conformational flexibility in the enzyme, a heterogeneity that must be taken into account when mapping active sites. The crystal structure of glycosomal holo glyceraldehyde phosphate dehydrogenase from *Trypanosoma brucei brucei* at 3.2 Å resolution is described. The overall conformation of the enzyme is similar but not identical to that of the enzyme from lobster and from *Bacillus stearothermophilus*.

In studies of the binding of molecules to streptavidin a comparison is made of the thermodynamic binding parameters and crystallographic studies for three structurally distinct classes of ligands, including *d*-biotin (the natural substrate), an azo dye and a streptavidin-binding peptide. This analysis led to suggestions on how to design better inhibitors. In a similar way, inhibitor binding to Ht-d metalloproteinase has been studied at 2 Å resolution. The use of *GRID* energy contour maps gave information on the substrate-binding pockets. The analysis is then extended to neutrophil collagenase, fibroblast collagenase and stromelysin. Results suggest Ht-d is a good model for design of novel inhibitors against zinc enzymes that degrade collagen, for example in wound healing. The crystal structure of porcine aldehyde reductase/NADPH binary complex at 3 Å resolution is reported. The enzyme is a β/α-barrel with the coenzyme binding at the carboxy terminus of the strands of the barrel. Inhibitors are also used in the treatment of diabetic complications.

The conference gave an overview of the current state of the art of structure-based drug design both in terms of methods used and in terms of the usefulness of the results.

We would like to thank the following organizations for their generous financial support of this meeting: the National Aeronautics and Space Administration, The National Institute of Allergy and Infectious Diseases, BioCryst Pharmaceuticals Inc., the DuPont Merck Pharmaceutical Company, Genentech Inc., Eli Lilly and Company, Merck Research Laboratories, Molecular Structure Corporation, the Procter and Gamble Company, Schering-Plough Research Institute, Warner-Lambert Company, and Bristol-Myers Squibb Pharmaceutical Institute. We also thank Penny Mann and Eileen Pytko for their day-to-day help with the organization and the management of the Conference, and Royal Cup Inc., of Birmingham, Alabama, for supplies.

Conference organizers
CHARLES E. BUGG
BioCryst Pharmaceuticals, Inc., Birmingham, Alabama, USA
LARRY DELUCAS
Center for Macromolecular Crystallography, University of Alabama at Birmingham, USA
JENNY P. GLUSKER
The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, USA