European Comission-sponsored COPERNICUS project:

Development of macromolecular X-ray crystallography and computer-aided modelling for genetic engineering and drug design in the Czech and Slovak Republics

Preface

Scientists throughout the world recognise that the knowledge of structure is essential to our understanding of molecular biology and related fields For effective studies in structural biology, resources and skills are needed in several related fields in molecular biology, biochemistry biophysics and X-ray or NMR techniques The results of these studies, and in particular the knowledge of three-dimensional structures of proteins, nucleic acids and other biologically interesting compounds, are essential for the development of computer-aided modelling, especially when concerned with drug design

The three-year European Comission sponsored programme, which began in February 1995, involved a network of 26 participating laboratories, nine from the European Union, twelve from the Czech Republic and five from Slovakia Since the practice of the methods used to determine three-dimensional structures of macromolecules was not well established in the Czech and Slovak republics, the programme included three hands-on workshops and numerous possibilities for exchanges in order to make them better known These workshops included crystallisation of proteins and nucleic acids, theory and practice of X-ray data collection and treatment using both laboratory and synchrotron radiation sources, methods of solving and refining macromolecular structures, molecular graphics and bioinformatics In addition to promoting the field of X-ray crystallography amongst the participating groups, methods of molecular modelling were exchanged and developed during the programme Scientists and research students from the Czech and Slovak Republics were given the means to visit laboratories of participants from the European Union to acquire or advance their know-how in these domains and to establish collaborations In particular, several groups, expert in molecular biology, biochemistry or biophysics, had the opportunity to become involved in structural studies, or to use the results of structural biology in a more informed manner

The final meeting of the COPERNICUS programme was a splendid opportunity to demonstrate the fruits of such a general approach The presentations of results covered all the aspects of the programme

important progress has been made in the elucidation of the structural basis of the HIV protease inhibition either in the form of active site inhibitors or monoclonal antibodies

– the structural analyses of RNases and their inhibitors has progressed with two new high-resolution X-ray structures

– in the related field of glucoamylases, significant progress has been made both in the biochemistry and in the structural analysis

– the determination of the structure of oligonucleotide analogues has been supplemented with molecular dynamics simulations in order to understand the properties of these analogues

– a similar approach has been adopted for the study of insulin and its semi-synthetic analogues the crystal structure of some of these was solved, in parallel with computer-aided modelling of the effect of the synthetic modifications

- the field of computer-aided drug design is heavily dependent on the availability of both suitable computers and suites of programmes, some of which are expensive The possibilities of collaborations offered by the programme were thus very useful and allowed progress in the studies of the delivery of drugs with the help of polymer carriers and the modelling of drugs acting on excitable membranes

– further developments using Patterson methods in small and macromolecular crystallography were pursued

– finally, several groups among the participating laboratories found common research themes that have allowed significant progress For example, several groups are interested in the understanding of the molecular mechanisms underlying the process of sporulation

While the European Comission-sponsored programme comes to an end, the interest in the field of structural biology will remain Many of the collaborations can and will continue to provide opportunities for interesting results as well as means for the training of scientists and students in the different techniques involved

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Structural Studies of HIV-1 Protease-inhibiting Antibodies

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The protease of Human Immunodeficiency Virus type 1 (HIV-1) is essential for the maturation of infectious viral particles (Katz and Kalka, 1994) It cleaves the Gag and Gag/Pol polyprotein precursors into the structural proteins and enzymes of HIV (including the protease itself) as well as some subsidiary polypeptides The enzyme is a homodimer belonging to the aspartate protease family in which the hydrophobic active site covered by two identical flap regions contributed by each of the respective monomers (Wlodawer *et al* 1989) The flap regions must undergo substantial conformational changes in order that the polyprotein substrate be bound at the active site of the enzyme (Fitzgerald and Springer 1991) The dynamic behaviour of the protease is therefore an essential element in understanding the function of the enzyme and its role in the viral life cycle We have studied the effect of monoclonal antibodies raised against HIV-1 protease to probe conformational changes that might be important for enzyme activity To this end,