ML-03.02 VIRUS STRUCTURE AND VIRUS INFECTION. By M. G. Rossman1, P. R. Kolaskar1, M. A. Oliveira1, R. Zhao1, T. S. Baker1, N. H. Olson1, R. H. Cheng2 and W. M. Greve3. 1Department of Biological Sciences, Purdue University, West Lafayette, IN 47907, USA; 2Institute for Molecular Biology, Pharmaceutical Division, MILES, INC., West Haven, CT 06516-4175.

A brief description of the crystallographic techniques used to determine virus structure and a short review of known virus structures will be followed by a presentation of recent results on the interaction of rhinoviruses with their receptors.

Cryo-electron microscopy has been used to determine the structure of human rhinovirus 16 complexed with its cellular receptor, the intercellular adhesion molecule-1. The receptor binds into a 12 Å deep "canyon" on the viral surface, confirming the prediction that the viral-receptor attachment site is in a cavity inaccessible to the host's antibodies. The atomic structure of human rhinovirus 16 and the structure of CD4 (homologous to intercellular adhesion molecule) 1 have both been determined and studied, therefore, for the crystallization of interferon. This research is enhancing the understanding of the virus-receptor complex.

A socket close to the site of receptor attachment can contain a cellular cofactor which can be replaced by antiviral agents. These antiviral compounds can inhibit viral attachment or uncoating. The overlapping binding sites of receptors and cofactor regulate the ability of a stabilised form of the virus to be transmitted between cells or for a destabilised form to enter the cell and thereby initiate infection.

ML-03.03 CRYSTALLOGRAPHY OF RIBOSOMES.

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Ribosomes are the universal cell organelle responsible for the translation of the genetic code into proteins. A typical bacterial ribosome contains more than one quarter of a million atoms and is of a molecular weight of 2.3 million daltons. It sedimentates with a coefficient of 70S and is composed of 3 clusters of RNA, a total of about 50 nucleotides, and about 75 deoxyribonucleotides. These are arranged in two independent subunits of unequal size (1.45 and 0.85 million daltons) which associate upon initiation of protein biosynthesis.

Intensive systematic exploration of crystallization conditions combined with individual testing led to reproducible formation of crystals of ribosomes, their complexes with components of protein biosynthesis, and natural, mutated and chemically modified (with an undegraded cluster) subunits. In all cases the crystallization conditions are chosen to be as close as possible to the natural environment of the ribosomes, and the crystalline ribosomal particles retain their integrity and biological activity for long periods in spite of the natural tendency of ribosomes to disintegrate and in contrast to the short life time of isolated ribosomes in solution. The most suitable crystals are of ribosomal particles from extreme halophilic and thermophilic bacteria. The highest resolution obtained so far is 2.9 Å.

The large unit cell dimensions, the extremely weak diffracting power, the relatively large mosaicity and the shape of the crystals (very thin plates or needles) dictates the performance of all steps in X-ray crystallographic analysis with intense and highly collimated synchrotron radiation. As ambient temperature, all crystalline ribosomal decay upon the first instance of X-irradiation. To overcome the severe sensitivity of these crystals to the X-ray beam, we developed cryo data collection techniques. These involve the determination of appropriate freezing conditions for each crystal form, shock cooling in liquid nitrogen at liquid nitrogen temperatures and data collection from crystals at about 40 K. Under these conditions the crystals are not damaged and stored for periods long enough for the collection of more than one data set.

The strategy of data collection and evaluation, the specific problems of these experiments and the quality of the results are described separately (Aymon et al., this volume). In general, the crystallographic data of these crystals is of a reasonable quality with X r.m.s. = 2.9% and adequate completeness.

ML-04.01 CRYSTALLOGRAPHIC ENVIRONMENT AS AN APPROACH TO MOLECULAR RECOGNITION AND DRUG-DESIGN. By Claudine Pascard I.C.S.N.-C.N.R.S. Gif-sur-Yvette, France

The molecular recognition process involved in drug design has been extensively studied over the last ten years. Thus, the structural information contained in large libraries such as the Cambridge Structural Database has been crucial in the process of finding new "lead" molecules. When the receptor site is known (by the X-ray structure determination of an inhibitor-receptor complex), the aim is to find a new ligand complementary with the binding site. With an unknown receptor, the strategy is to identify the pharmacophore, to use its stereo and physicochemical features for mapping the receptor site, and a search is then made for other ligands using recently developed 3D-search programs, in conjunction with crystallographic data banks. Examples of these strategies which have accelerated the research for more potent drugs will be presented.

However, crystallographic results must not be reduced to a source of three-dimensional coordinates. The solid state medium is as rich in structural informations as both the solution state and ab initio calculations. Very valuable informations on desirable active conformation can be retrieved from various crystal structures of a given family of active compounds, wherein the different interactions molecule-solvent, and/or molecule-ion can be compared. These points will be discussed.