given rise to a picture in which the virus is a metastable intermediate which links virus assembly and cell-entry. In this model the cleavage of VP0 and subsequent rearrangements of VP4 and the aminoterminal extension of VP1 trap the virus in the metastable form and prime it for subsequent structural rearrangements required for cell-entry. The receptor "catalyzes" these transitions by utilizing some of the energy which is released upon its binding to receptor to lower the activation barrier which traps the virus in this metastable state (2).

In order to further characterize this process we have undertaken a program of structural studies of intermediates which are thought to be important in the cell entry process using cryoelectron microscopy (in collaboration with Alasdair Stevens, Frank Booy, Benes Trus and David Belnap at NIH) and x-ray crystallography. Low resolution models for two such intermediates will be presented.

MS04.09.02 THE STRUCTURE OF INTACT HUMAN RHINOVIRUS 14 COMPLEXED WITH Fab17-IA. Thomas J. Smith, Elaine S. Chase, Timothy Schmidt, Norman H. Olson, Timothy S. Baker, Department of Biological Sciences, Purdue University, West Lafayette, IN 49707

Antibodies are a major component of the immune response to picornaviruses. It has long been contended that antibody neutralization is due to large structural changes in the capsid upon binding. To test this hypothesis, we have used crystallography and electron microscopy to determine the structure of intact human rhinovirus (HRV14) complexed with Fab17-IA. The atomic structures of Fab17-IA and HRV14 were first used to interpret the ~25Å resolution image reconstruction. This model was used to calculate initial phases to 8Å resolution for the data from a frozen Fab17-IA/HRV14 crystal. After phase extension to 4Å resolution, the structure clearly shows that the initial model was mis-positioned by up to 4Å in places, the HRV14 structure does not seem to change upon antibody binding, and that the CDR3 loop of the heavy chain moves to accommodate the epitope. This CDR3 movement had been predicted by molecular dynamics calculations.

MS04.09.03 STRUCTURAL STUDIES ON ORBIVIRUSES. J. Grimes[1], P. Gouet[1], A. Basak[5], G. Sutton[1,2], P. Roy[1,2], N. Burroughs[3], B.V.V. Prasad[4], P. Mertens[3] and D. Stuart[1], [1]Laboratory of Molecular Biophysics, Rex Richards Building, South Parks Road, Oxford, OX1 3QU, United Kingdom, [2]NERC Institute of Virology, Mansfield Road, Oxford, United Kingdom, [3]Institute for Animal Health, Pirbright, Surrey, United Kingdom, [4]Baylor College, Houston, Texas, USA, [5]Birkbeck College, Malct St., London, United Kingdom

We are studying the structures of some orbiviruses. These are animal viruses, which belong to the same family as the better known rotaviruses and reoviruses, which cause significant human disease[1]. Bluetongue virus is the classic orbivirus; it has a proteinaceous capsid from which an outer layer can be stripped away to reveal a 700Å core particle[2]. The core is robust and penetrates the host cell intact, it contains a small number of proteins with enzymatic activity and much larger numbers of VP3 and VP7. VP7 forms the outer surface of the core and is present at the level of 780 copies per core, arranged on a T=13 lattice[2]. We have determined, by X-ray crystallography, a number of structures of this molecule[3] (Grimes et al., unpublished). We have combined the information from the X-ray structures of VP7 with that from electron cryo-microscopy (Prasad, unpublished) and used simple fitting procedures to place the X-ray structure in the EM map.

We have separately crystallized the whole core of 2 serotypes: BTV-1 and BTV-10. BTV-1 crystallized in space group $P2_12_12$, a=798Å, b=825Å, c=756Å, BTV-10 crystallized in space group $P4_12_12$, a=b=1120Å, c=1592Å. Data have been collected at the SRS (UK) & ESRF (Fr) for BTV-1 and at the ESRF for BTV-10. Both structures have been solved at low resolution using the cry-EM phasing model. The resolution is being extended for both structures and the unusual architecture will be discussed.

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[2] Prasad, B.V.V. et al., J.Virol., 66, 2135-2142 (1994).
[3] Grimes, J. et al., Nature, 373, 167-170 (1995).
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MS04.09.04 STRUCTURES OF INFLUENZA VIRUS PROTEINS. Ming Luo, University of Alabama at Birmingham, 1918 University Blvd., Birmingham, AL 35294

We have determined the structure of type B influenza virus neuraminidase. Influenza virus infection remains to be an uncontrolled human disease which causes up to 20,000 death per year. Novel inhibitors guided by the crystal structure of NA from several virus strains have been developed and structures of NA complexed with various inhibitors are reported here. These compounds (benzoic acid derivatives) are aromatic in nature and offer the advantages of chemical stability and simplicity in chemical synthesis. They also have the potential to be orally active. 13 compounds have thus far been designed and synthesized. The most potent inhibitor synthesized so far has an IC_{50} value around 2 μM in NA enzyme inhibition assays and was shown to reduce influenza virus HA titer in cell culture by 50% at a concentration between 1 - 10 μM. Since a large number of compounds representing different chemical classes have been prepared, they can be quickly screened when new strains emerge in a pandemic. If they are not effective, we can model the new strain based on existing NA structures and come up with new modifications. Since aromatic compounds are easier in chemical synthesis, this process can be fast.

In addition, we are working on the structure of other influenza proteins which can be potential targets for structure-based drug design. Currently, we have grown crystals of M1 and are in the process of determining the structure. M1 is relatively more conserved when compared with NA. With drugs targeted to different proteins, we have a better chance to handle a pandemic.

MS04.09.05 THE STRUCTURE OF TURNIP YELLOW MOSAIC VIRUS (TYMV) AT 3.2 Å RESOLUTION. M. A. Canady, S. B. Larson, J. Day, and A. McPherson, Department of Biochemistry, University of California, Riverside CA 92521 USA

The structure of turnip yellow mosaic virus has been solved to 3.2 Å using molecular replacement, multiple isomorphous replacement (MIR), and molecular averaging. Crystals were of space group $P6_422$ with unit cell dimensions a=b=515.5, c=309.4 Å. Native and heavy atom data were collected at Brookhaven National Laboratory at the University of California, San Diego. Using cowpea chlorotic mottle virus as a model, phases were computed and the map was averaged. A difference Fourier synthesis using the phases from the averaged map and data collected from two platinum derivatives allowed us to determine the positions of the heavy atoms. A polyalanine model was built into an averaged MIR map. Correct sidechains were built into an averaged map phased by the refined polyalanine model. The structure was refined using conjugate gradient minimization, simulated annealing, and individual restrained B factor refinement to an R-value of 18.7% with a free R-value of 19.3% to 3.0 Å. The structure of the virion at high resolution resembles the predictions made at low resolution, with the pentameric and hexameric coat protein assemblies