



# overview

Advances in Structural Biology have accelerated greatly as a result of access to the synchrotron facilities that have been developed around the world in the past 25 years.

Pharmaceutical and bioscience companies have been swift to recognise the huge commercial potential that lies behind understanding the multitude of processes that take place within living organisms at a molecular level.

Researchers in the UK are at the forefront of this work, using macromolecular crystallography to study areas such as macromolecular assemblies, cell cycle progression, viruses, the immune system, the structure of membrane proteins and genomics, often using the results for rational drug design.

## Key Challenges

- **Unlocking the secrets of protein structures and whole cells**  
Knowing the structure of proteins may reduce the cost of drug development by up to a factor of ten. This could lead to the development of many more much needed new drugs.
- **Immune system studies**  
Proteins involved in inflammatory and immune responses are key targets for X-ray crystallographic analysis..
- **Membrane proteins**  
Almost 50% of drug compounds in clinical use are targeted at membrane proteins. Consequently, structural studies in this area are becoming increasingly important
- **Natively disordered structures**  
30-50% of proteins of eukaryotic cells have natively disordered structures that cannot be crystallised. These proteins are important in signal transduction of normal and tumour cells, so in solution studies are crucial to investigate these systems.

## The Synchrotron Solution

The structural biology research community is expanding and Diamond wants to encourage further growth as a result of the unique capabilities it will offer.

Highly efficient and productive beamlines will offer robotic systems for automated sample handling and crystal centring, and software allowing automated data collection.

## Techniques

The three Phase I Macromolecular Crystallography beamlines will all be tunable over the wavelength 0.5Å – 2.5Å to enable Multiwavelength Anomalous Diffraction (MAD) experiments to be carried out.

In addition, Microfocus Macromolecular Crystallography beamline, Circular Dichroism, Powder Diffraction and Single Crystal Diffraction will be available.

**Beamlines:** I02, I03 & I04 Macromolecular Crystallography, I24 Microfocus Macromolecular Crystallography, B23 Circular Dichroism, I11 High Resolution Powder Diffraction and I19 Single Crystal Diffraction

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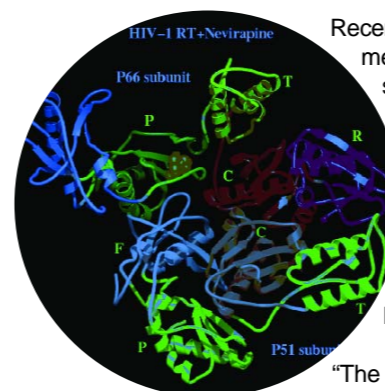
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# case studies

## Drugs for HIV

Research on understanding the structure and function of the HIV protein called reverse transcriptase (RT), which the majority of anti-AIDS drugs target, began back in the late 1980's. Structural determination is vital in the quest to develop better drugs to treat HIV.



Recent developments in X-ray crystallography methods have helped researchers to make some important discoveries and various synchrotron light facilities around the world have become invaluable tools for the teams working in this area.

Prof David Stammers of the University of Oxford, leads a group at The Wellcome Trust Centre for Human Genetics where HIV forms part of the research programme.

"The crystal structures of HIV RT that have been solved with the help of synchrotron light have gone some way to telling us how the drug resistance comes about", explains Prof Stammers.

"Additionally, the structures have provided the basis for the design of new non-nucleoside inhibitors which retain high potency against existing drug resistant forms of the virus. It is hoped that the inhibitors will form the basis for the next generation of anti-HIV RT non-nucleoside drugs".

Source: Prof David Stammers [www.strubi.ox.ac.uk](http://www.strubi.ox.ac.uk)

## Pressing problems

During production pharmaceutical drugs undergo a range of processes, including drying, granulation, milling and compression. As a result they are exposed to changes in temperature, pressure and relative humidity, all of which may affect the properties of these drugs. This includes the creation of polymorphs – substances with the same chemical composition, but different crystal structures.



The process of compressing drugs into tablet form can create new polymorphs. As a result it is necessary for pharmaceutical companies to understand the forces within the crystal structure, to predict the properties of the polymorphs after processing. It may also be possible to create new polymorphs with desirable characteristics, for example good solubility.

By studying solvate formation in high pressure cells it has been possible to isolate particular solvates and adducts of common pharmaceutical drugs, for example paracetamol and zopiclone and structurally characterise them using single crystal diffraction and powder diffraction techniques on a synchrotron.

Significantly these techniques could establish structures of pharmaceuticals from first principles.

In future new polymorphs of pharmaceutical compounds may be developed using these techniques, to produce more effective drugs and improve understanding of production processes.