

High performance computing was used to investigate the effects of resistance mutations within a crucial enzyme of Human Immunodeficiency Virus (HIV) towards the antiviral drug Nevirapine.

<<< Molecular Modelling of HIV Reverse Transcriptase

Human Immunodeficiency Virus (HIV) currently affects approximately 40 million people worldwide and although a number of antiviral drugs are available for treatment, the virus often develops resistance to these medications. Changing to alternate drugs can often lead to further resistance until no drug choices remain for the patient, and thus can not be used as a long term strategy to overcome this issue. As it is difficult to predict what resistance mutations will arise upon starting a new antiviral treatment, it is desirable to have a model system upon which to test the existing range of drugs to assess which drug is most suitable to treat that particular strain of the virus.

HIV reverse transcriptase (HIV rt) is a crucial enzyme involved in the replication of HIV. The HIV rt itself is made of two subunits, p66 and p51, which catalyse the reverse transcription of viral RNA into DNA. This new viral DNA is then integrated into the host DNA by the virus, establishing a long term infection.

Certain anti-HIV drugs such as Nevirapine target HIV rt, but their use in treatment often leads to drug resistance due to viral mutation. One mutation in particular, N348I, was conveying broad resistance towards non-nucleotide rt inhibitors. The reason for this resistance, however, was not immediately intuitive as the position of the mutation was reasonably distant from the drug binding site.

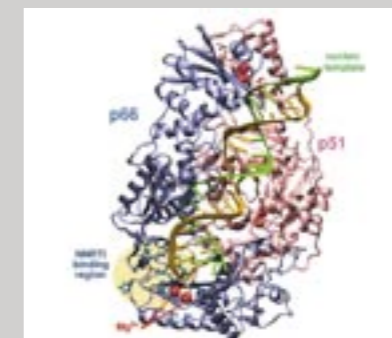
HIV rt Modelling using HPC

VPAC's participation in the project allowed researchers at the Burnet Institute to visualise the HIV rt as a 3 dimensional model. The model was then used in subsequent molecular dynamics simulations which started to reveal movements and domain shifts which are important in HIV rt activity. By making the same mutations in the model that are observed clinically, and subjecting the model to further molecular dynamics simulations, it became apparent that the N348I mutation is involved in a "hinge" region of the thumb domain. Interference of the thumb domain appears responsible for conferring drug resistance by potentially loosening the drug binding pocket.

The modelling of HIV rt performed by VPAC proved useful in the investigation of other resistance-related mutations and provided a platform useful in exploring possible HIV rt mechanisms.

This project was undertaken in collaboration with Dr Gilda Tachedjian, Burnet Institute (www.burnet.edu.au). For further information regarding the molecular modeling techniques used in this project, contact Dr Mike Kuiper at VPAC via mike@vpac.org or phone +61 3 9926 4645.

Image on left: N348 interaction with the thumb domain of HIV reverse transcriptase



HIV reverse transcriptase model showing NNRTI and nucleic acid binding region



Dimerisation interface of the HIV reverse transcriptase enzyme