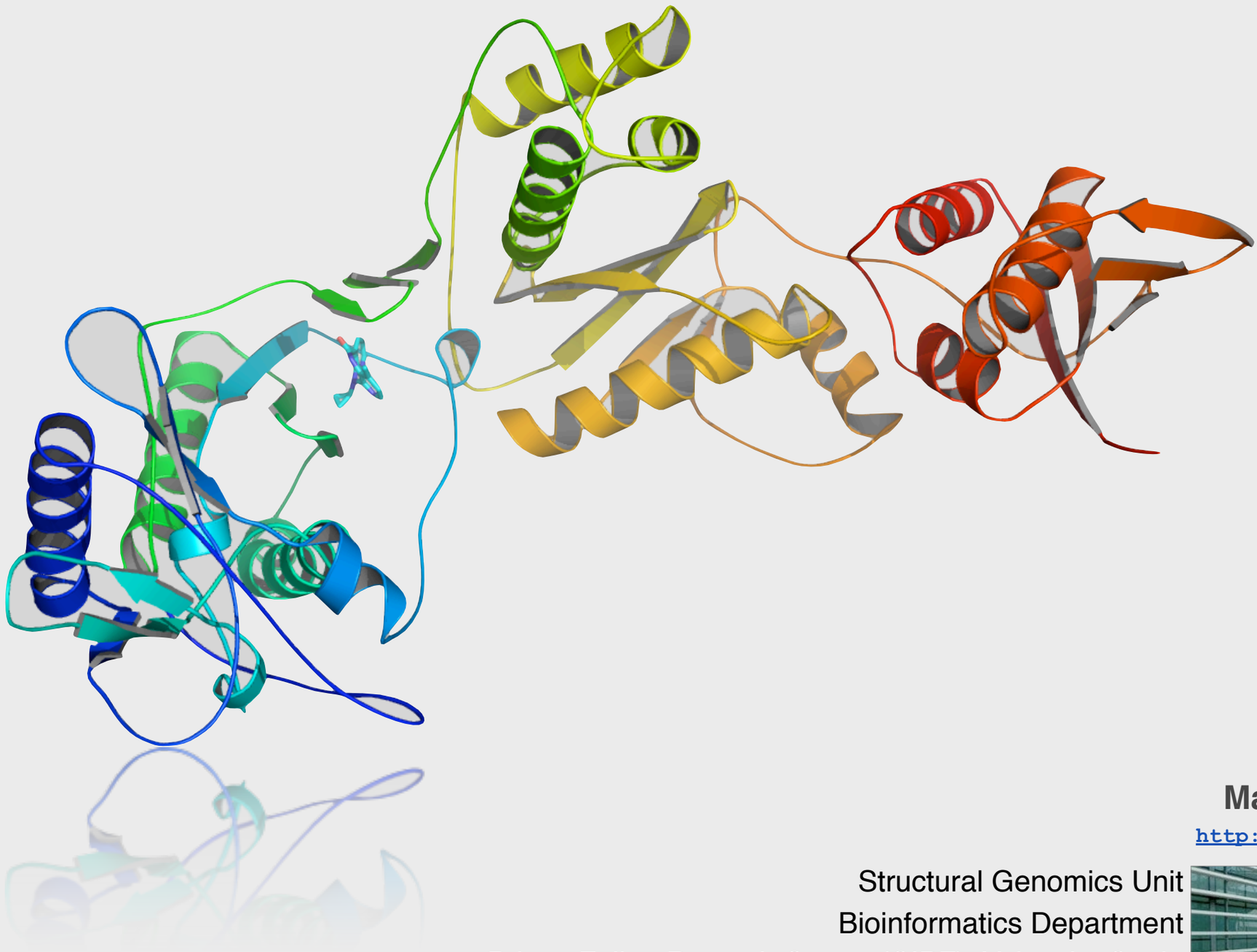
Exercise. SNP-based drug resistance to Nevirapine drug against the HIV reverse transcriptase



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Problem

TO STUDY THE EFFECT IN BINDING OF KNOWN SNPs OF HIV REVERSE TRANSCRIPTASE

TOOLS

- AnnoLyze (DBAli)
- PubChem and DrugBank
- MODELLER
- AutoGrid, AutoDock, and AutoDockTools
- PyMol

Organization

L100I

V106M

V108I

Y188C

Input data and files

Mutation paper

Volume 16 Issue 1 March/April 2008

Update of the Drug Resistance Mutations in HIV-1: Spring 2008

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This Spring 2008 version of the International AIDS Society–USA (IAS-USA) Drug Resistance Mutations Figures updates the figures published in this journal in August/September 2007.[1] The authors comprise the IAS-USA Drug Resistance Mutations Group, an independent, volunteer panel of experts charged with the goal of delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. As for all IAS-USA panels, a rotation procedure is in place whereby 1 or 2 panel members periodically step down from panel participation and new members join. These rotations are designed to ensure that all IAS-USA expert panels remain diverse in member affiliations and areas of expertise.

The figures are designed for practitioners to use in identifying key mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Updates are posted periodically at www.iasusa.org. Care should be taken if using this list of mutations in surveillance or epidemiologic studies of transmission of drug-resistant virus. Some amino acid substitutions, particularly minor mutations, represent polymorphisms that in isolation may not reflect prior drug selective pressure or reduced drug susceptibility.

The mutations listed have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. The group reviews data that have been published or have been presented at a scientific conference.

Drugs that have been approved by the US Food and Drug Administration (FDA) as well as any drugs available in expanded access programs are included. They are listed in alphabetic order by drug class. User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral therapy history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance most commonly develops to lamivudine or the nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]). The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, nonadherence to medications, laboratory error, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

Revisions to the Figures for the Spring 2008 Update

In addition to minor formatting and color alterations, revisions to the figures include removal of the "expanded access" indication for etravirine because the drug was approved by the US FDA in early 2008. A new etravirine mutation, V179T, has been added to the figure bar, and user note 13 has been revised to reflect new information concerning etravirine mutations. Also, the expanded access indication for raltegravir has been removed because the drug was approved by the US FDA in late 2007.

Comments?

The IAS-USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes.

(continued, page 67)

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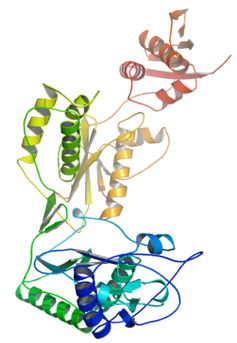
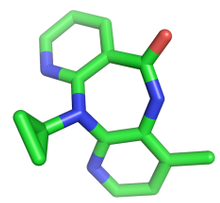
Structure files





Sequence and alignment files

```
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QSSMTKILEPFRKQNPDIVIYQYMDDLYVGSDLEIGQHRTKIEELRQHLLRWGLTTPDKKHQKEPPFLWMGYELHPDKWT
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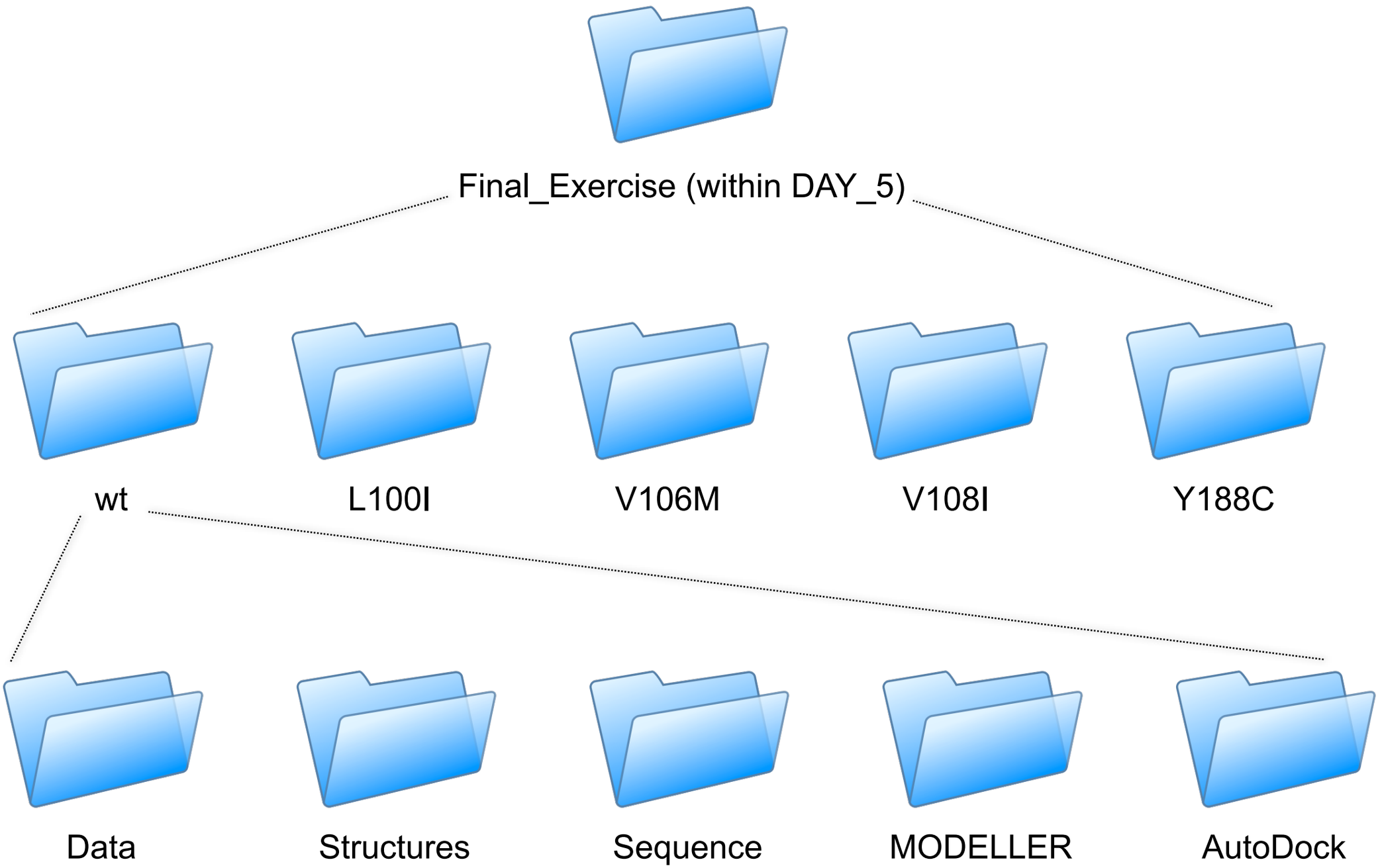
Folder organization



Recipe

LIGAND

1. Go to PubChem and look at Nevirapine (NPV). Smile it!.
2. Divided by groups:
   a) Get similar compounds with a Tanimoto score larger than 95%. Download the SDF files.
   b) Do a sub-structure search based on the SMILES. Download the SDF files.
   c) Do a sub-structure search + filter by molecular weight (200-600Da). Download the SDF files.
   d) Do a super-structure search + filter by molecular weight (200-400Da). Download the SDF files.

BINDING SITE

1. Run AnnoLyze for the chain 1vruA.
2. Get predicted binding site to Nevirapine (NVP ligand).
3. Calculate a central point to the ligand using PyMol (see *boxing.txt* file under data folder).

COMPARATIVE PROTEIN STRUCTURE PREDICTION

1. Model the 3D structure of the wild-type using its own structure.
2. Model the point mutation for your group.

DOCKING OF SMALL MOLECULES

1. Dock the NVP ligand to the wild-type model.
2. Dock the NVP ligand to the mutant.

PRESENTATION

1. How would you explain the differences between the wild-type and the point mutant?