Methionine Aminopeptidase 1 Docking for Inhibitor Candidacy

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Abstract

Methionine Aminopeptidase 1 (Met AP 1) is a widespread enzyme found in *Rickettsia prowazekii*, a parasitic bacteria that causes typhus and other diseases. As such, it is critical to find the active site of MetAP1 on *Rickettsia prowazekii* in order to determine inhibitors through protein-ligand binding. The program DockBlaster uses docking as a molecular modeling technique in order to predict the orientation of a ligand when binding to an enzyme. The PDB code for MetAP1 from the RCSB database along with the corresponding ligand, glycerol, is submitted into DockBlaster. After virtual screening, it was determined that MetAP1 contains six pockets available for docking, and the active site was discovered. In a future study, inhibitors can be determined and tested for interactions with MetAP1, which would provide direction on antibiotic drug candidacy and development.

Aim

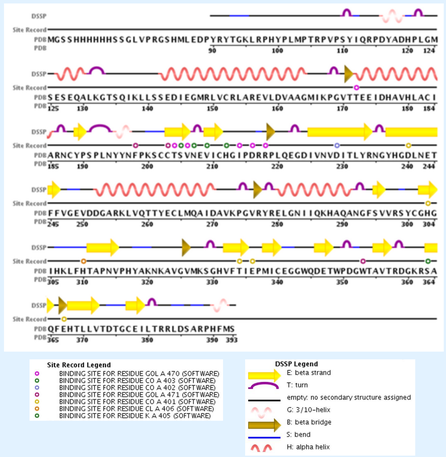
Rickettsia prowazekii is a gram-negative cocci bacteria that causes typhoid fever and other diseases. Typhoid fever is endemic in areas of large homeless populations, and is spread through body lice and tick bites.[2] MetAP1 is a ubiquitous and necessary enzyme in prokaryotic bacteria *Rickettsia* and is therefore crucial to terminate its activity.

The aim of this experiment is to locate the active site of MetAP1 through the use of molecular modeling. This provides a visualization for the orientation of inhibitors, which can provide screening for future antibiotic drug candidacy and development against *Rickettsia prowasekii.*

Method

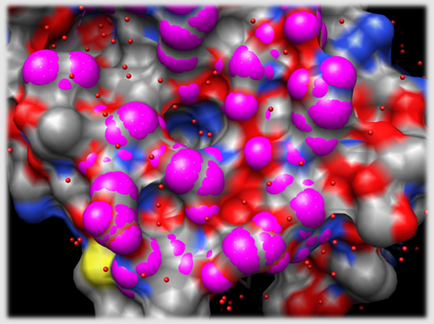
- Obtain the 4-character PDB code for Met AP 1 in the RCSB database (2B3H)[1]
- Identify the suitable ligands associated with the binding sites of MetAP1 (GOL: glycerol)
- Submit both the PDB code and the corresponding ligand to DockBlaster for docking, and run the program[4]
- Use UCSF Chimera Molecular Modeling System to obtain a virtual rendering of the pockets of MetAP1
- Determine the location of the active site of the enzyme for inhibitor binding based on the pockets available from the virtual screening; this determines the appropriate orientation for inhibitor drug candidacy

MetAP1 Secondary Structure
Source: RCSB Protein Data Bank



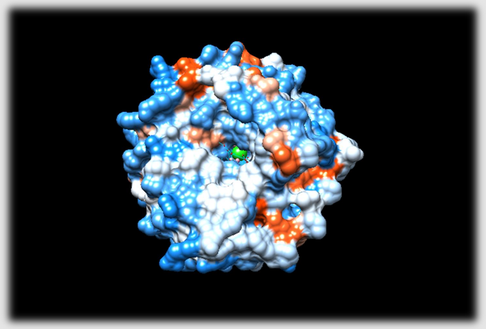
MetAP1 Polymer Sequence
Source: RCSB Protein Data Bank

Results



MetAP1 Active Site
Source: DockBlaster

- DockBlaster results: when the small ligand chlorine ion (Cl-) was input the docking system would not run, however, successful docking was achieved with the larger ligand glycerol (GOL)
- Six pockets were found in MetAP1 (pocket 2.1 shown below)
- Chimera System provided successful clear visualization of the active site (shown in green)[5]



MetAP1 Active Site
Source: UCFS Chimera

Conclusion

The six pockets provide binding sites for inhibitors. The active site was determined using glycerol as the ligand.

In future study, molecular inhibitors can be determined using the orientation of the active site. This would provide the basis for experimentation with *in vitro* enzymatic assays for MetAP1-inhibitor interactions and future antibiotic development.[3]

References

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5. MetAP1. (n.d.). Retrieved March 3, 2015, from http://www.cgl.ucsf.edu/chimera/

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