# STEM Scholars program 2013

## COMPUTATIONAL DRUG DESIGN

Search for novel inhibitors of Adenosine Deaminase(ADA)

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## Abstract

Computer aided drug design is an effective strategy for accelerating and economizing the drug discovery and development process. Adenosine Deaminase (ADA) is involved in purine metabolism which catalyzes the irreversible deamination of adenosine and deoxyadenosine to inosine and deoxyinosine(1). Computational methods such as molecular docking, pharmacophore modeling, and molecular similarity calculations have been improved last decades and can be utilized to predict key features of possible drugs. In this study a retrospective search of known binders to ADA was conducted using a pharmacophore developed from known ligands of ADA. The pharmacophore was found to be a good predictor of binding affinity, yielding an enrichment factor of 5.83.

## Introduction

Small molecules inhibitors are drugs that prevent a protein from functioning by binding and hence blocking the active site of that protein. A pharmacophore is an abstract 3-D model that attempts to represent the essential molecular features that are important for binding to a given protein's active site. The pharmacophore can then be used to computationally search through large databases of molecules and identify molecules that share these features and can potentially bind to that target. The goal of this project is to come up with a technique that can help identify novel inhibitors of ADA. ADA inhibitors are cytotoxic immune system suppressors however they are used therapeutically in the treatment acute leukemia and in the diagnosis of immune deficiency disorders (2).

## Material and Methods

- MOE ( Molecular Operating Environment ) is a three dimensional software.
- To create pharmacophores MOE's pharmacophore elucidation software was used, pharmacophores were built based on a feature alignment alorithm.
- Ligands were docked using MOEdock, on rigid systems utilizing the Triangle matcher placement algorithm and london dG scoring functions.
- VMD (Visual Molecular Dynamics) is a software package for three dimensional visualization, modeling and analysis of molecular systems.

## Results

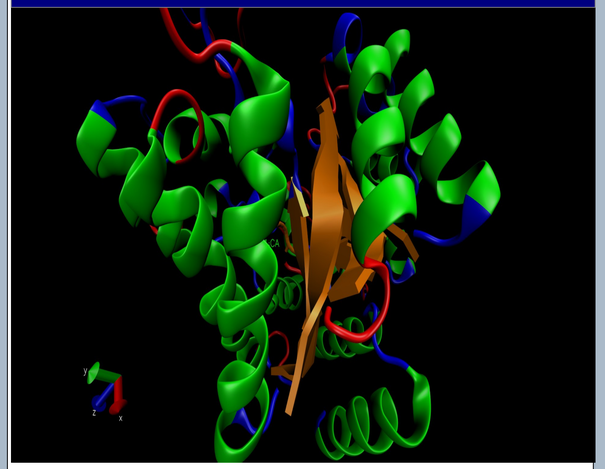

Fig 1. VMD Visualization of different structural elements of ADA:code 1NDV showing alpha helix(green), beta-sheet (yellow),and turns(red)

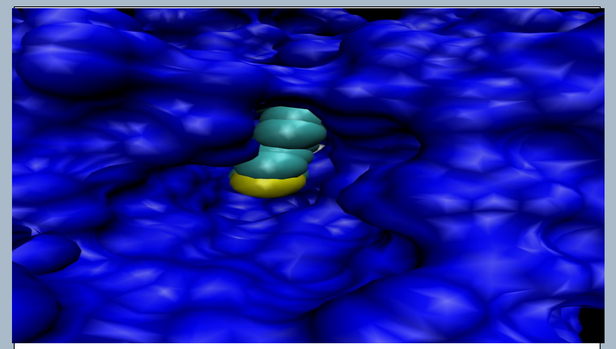

Fig 2. VMD Surface representation of the receptor (blue) with a bound ligand FR117016 (green).

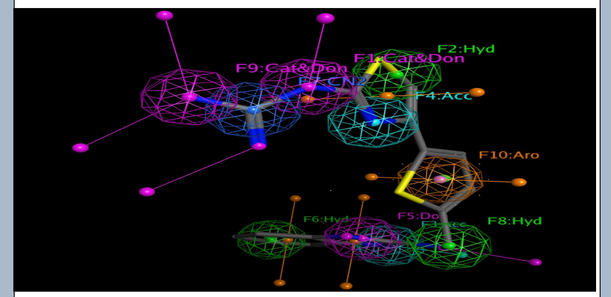


Fig 3. MOE Visualization of the pharmacophore of the binding ligand FR117016

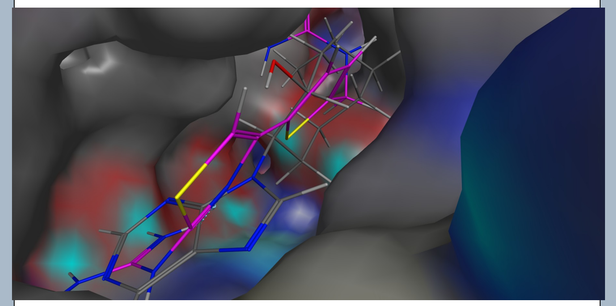

Fig 4. Representation of the docked ligand FR 117016(purple) and the top ranked screened compound (blue) from the database search.

## Conclusion

Adenosine deaminase is an important protein in the development and maintenance of the immune system and epithelial cell differentiation(3). Computational drug design is a useful tool in terms of scientific research and holds the promise of helping design less expensive and more effective drugs. The methods reviewed here may help discover new drugs and can be applied to other protein targets.

## References

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2) Sanchez JJ, Monaghan G, Borting C, Norbury G, Gaspar HB (2007)."ADA -deficient severe combined immunodeficiency(SCID) Pt3: 336-47

3) Moriwaki, Y.; Yamamoto, T.; Higashino, K. (1999). "Enzymes involved in purine metabolism--a review of histochemical localization and functional implications". Histology and histopathology 14 (4): 1321–1340

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