

High-Throughput Computational Drug Design Targeting Deadly Viruses

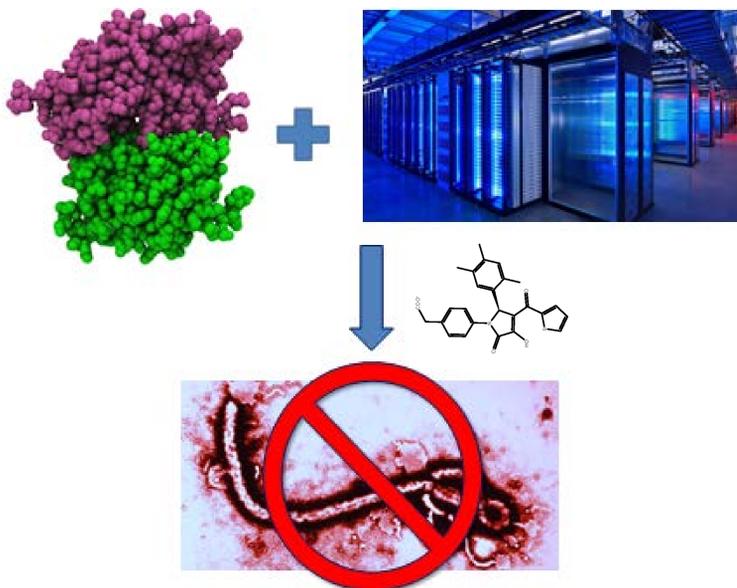


S&T Campaign: Computational Sciences
Predictive Sciences

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Research Objective

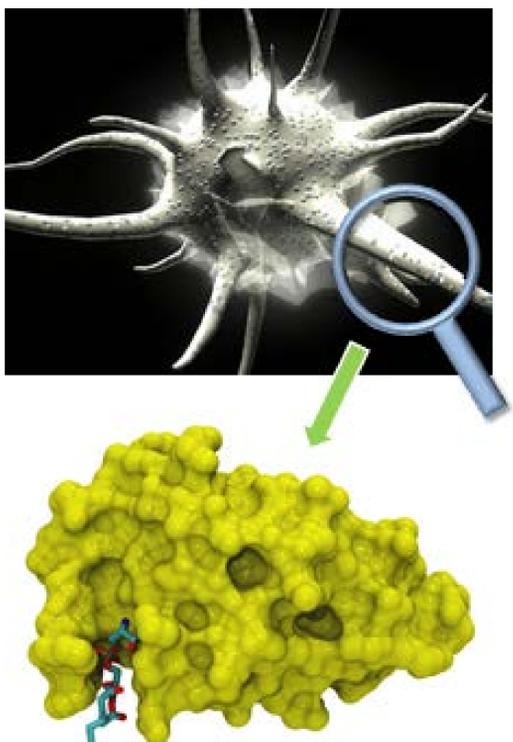
- Find novel therapeutics against biodefense pathogens (e.g., Ebola virus) using high performance computing to sort through *millions* of candidates



We are using a supercomputer to find small molecules that will inhibit the molecular dimer of Ebola protein (magenta) and host protein (green) to stop spread of the Ebola virus in humans

Challenges

- Theoretical predictions of drug efficacy must be improved as current hit rates < 20%.
- We also need to predict whether drugs will be safe in humans.



We are also computationally screening the binding pocket of a human membrane receptor protein to find small molecules that will prevent entry of Ebola and other viruses into host cells (dendritic cell in picture.)

ARL Facilities and Capabilities Available to Support Collaborative Research

- We use in-house/non-commercial computational docking, molecular dynamics and molecular visualization software.
- We have ongoing collaborations with structural biologists and molecular virologists in academia and government.
- Our lead compounds are being optimized towards real-world therapies.
- We have a number of success stories in early-stage computational drug discovery:

- Han Z et al. Small Molecule Probes Targeting the Viral PPxY-Host Nedd4 Interface Block Egress of a Broad Range of RNA Viruses *J. Vir.* 88 (13), 7294-7306 (2014)
- Brown, CS et al. *In Silico* Derived Small Molecules Bind the Filovirus VP35 Protein and Inhibit Its Polymerase Cofactor Activity, *J. Mol. Bio.* 426 (10), 2045 (2014)
- Lu J et al. A Host-Oriented Inhibitor of Junin Argentine Hemorrhagic Fever Virus Egress. *J Vir.* 88 (9) 4736 (2014)
- Swietnicki W et al. Identification of small-molecule inhibitors of Yersinia pestis Type III secretion system YscN ATPase. *PLoS ONE* 6 (5), e19716 (2011)

Complementary Expertise/ Facilities/ Capabilities Sought in Collaboration

- X-ray crystallography
- Nuclear magnetic resonance
- Enzymology
- Surface-plasmon resonance
- Molecular biology
- Protein chemistry
- Synthetic organic chemistry
- Computational methods development