Novel Drug Design for *Chlamydia trachomatis*

David Liang, Gurasees Bajaj, Neil Patel, Shreya Sriram, Shreya Karpoor

Dr. Oscar Juarez, Life Sciences Department

Illinois Institute of Technology

Background

Chlamydia trachomatis is an obligate intracellular, gram-negative bacteria that causes the disease chlamydia, one of the most common STDs in the US and is the leading cause of trachoma. The CDC reported nearly 1.6 million cases of chlamydia in 2015 alone. Chlamydia was initially thought to be an “energy parasite”, unable to produce its own energy; however, recent studies have shown that chlamydia possesses the metabolic enzymes required for respiration. One enzyme called PFK partakes in the rate-limiting “committed” step of glycolysis, controlling the continuation of respiration. Chlamydial PFKa1 and PFKa2 are distinct from mammalian PFK as PFKa1/2 are pyrophosphate-dependent instead of ATP-dependent, making PFKa1 and PFKa2 prime targets for drug development.

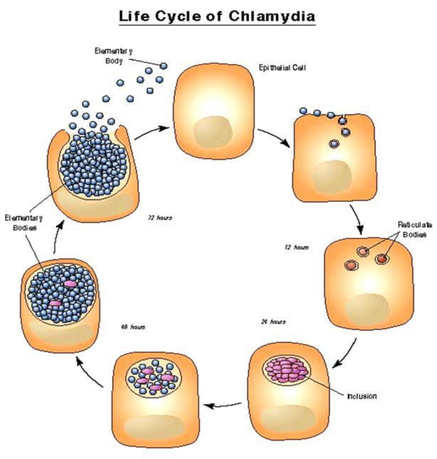


Fig. 1. Life cycle of *C. trachomatis* infecting a human cell.

Objectives

- Create models of PFKa1 and PFKa2
- Using the models to select the best potential competitive inhibitors
- Analyze impact of inhibitor on PFK reaction rate

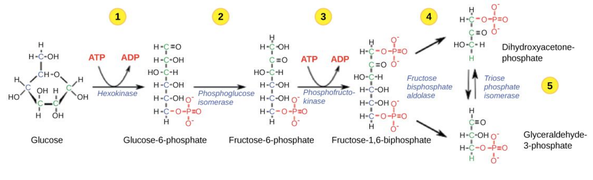


Fig. 2. Phosphofructokinase catalyzes the “committed” step of glycolysis. Once the reaction has occurred, glycolysis must continue.

Modelling Results

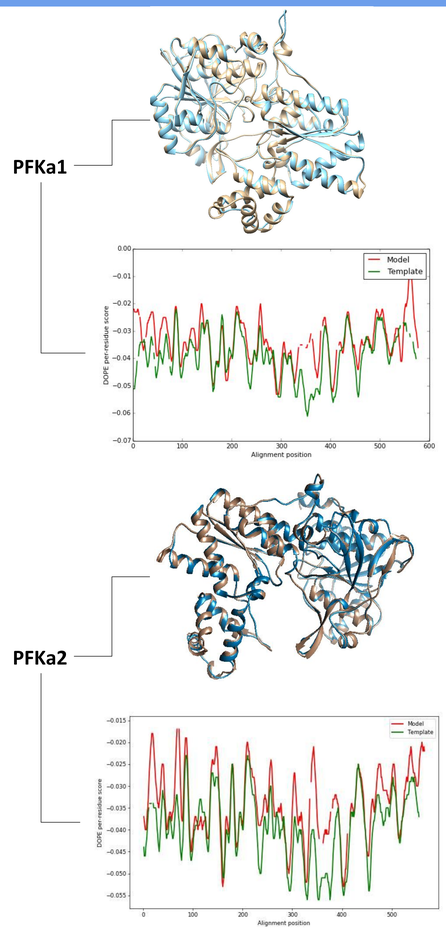
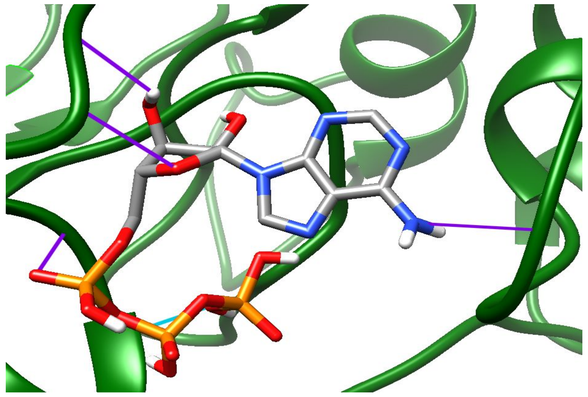


Fig. 3. a) Generated PFK model based off of a PFK from *B. burgadorferi (*Tan=Borrelia, Blue=Chlamydia). Overlapping sections means the model fits. b) Residue graph determining similarity at various sites. Overlapping sections between red (Chlamydia) and green (Borrelia) mean similarity.

Docking Results



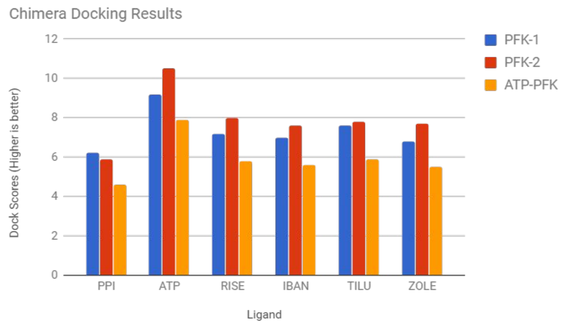


Fig. 4. a) Ligand docking simulation using UCSF Chimera. Purple lines are hydrogen bonds. Blue molecule is modelled PFK. Red and orange molecule is the phosphate group of a bisphosphonate. b) Graph of dock scores using UCSF Chimera AutoDock Vina. Binding affinity and hydrogen bond potentials are calculated and scored. Higher dock scores mean better potential bonding.

In vitro Testing Results

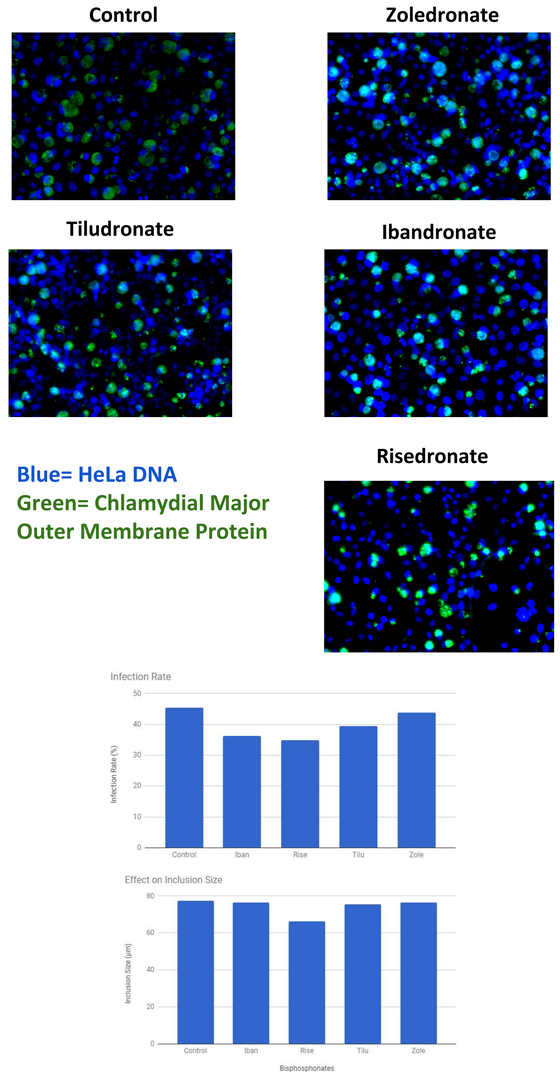
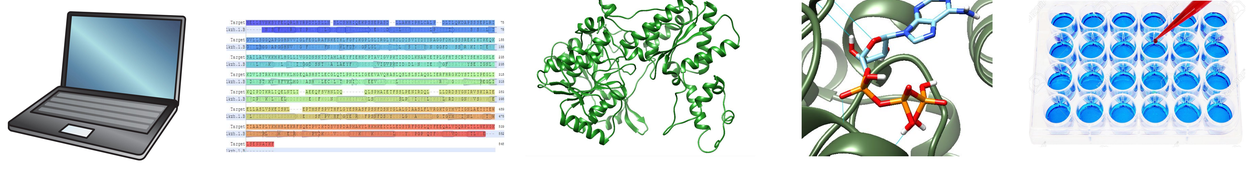


Fig. 4. a) 50ml of 200mM bisphosphonates were added to stained infected HeLa cells. Pictures were taken under fluorescence microscope. b) Inclusion size and infection rate were measured by hand.

Methodology



Compare sequences against PubMed Database → Align PFKa1/2 sequences with other proteins → Generate model based off of alignment → Dock bisphosphonates onto model → Analyze impact of drugs on activity

References

1. Boyer, R. F. (2012). *Biochemistry laboratory: Modern theory and techniques*. Boston: Prentice Hall.
2. Omsland, A., Sixt, B. S., Horn, M., & Hackstadt, T. (2014). Chlamydial metabolism revisited: Interspecies metabolic variability and developmental stage-specific physiologic activities. *FEMS Microbiology Reviews FEMS Microbiol Rev, 38*(4), 779-801. doi:10.1111/1574-6976.12059