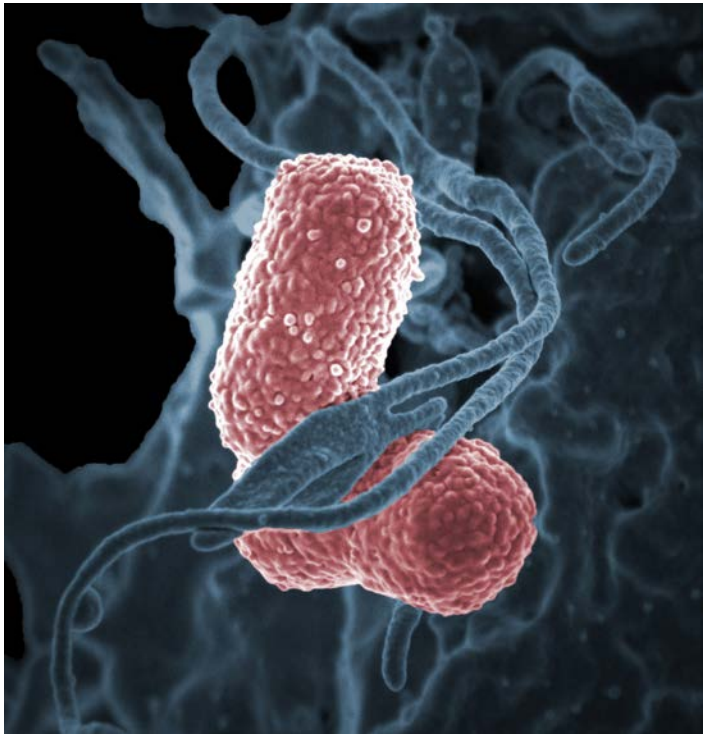
Computational Modeling Identifies Biosynthetic Modifications to Improve Drug Inhibition Against *Klebsiella pneumoniae*

By Kara Luo
MIT PRIMES 2016
Mentored by Gil Alterovitz

Klebsiella pneumoniae

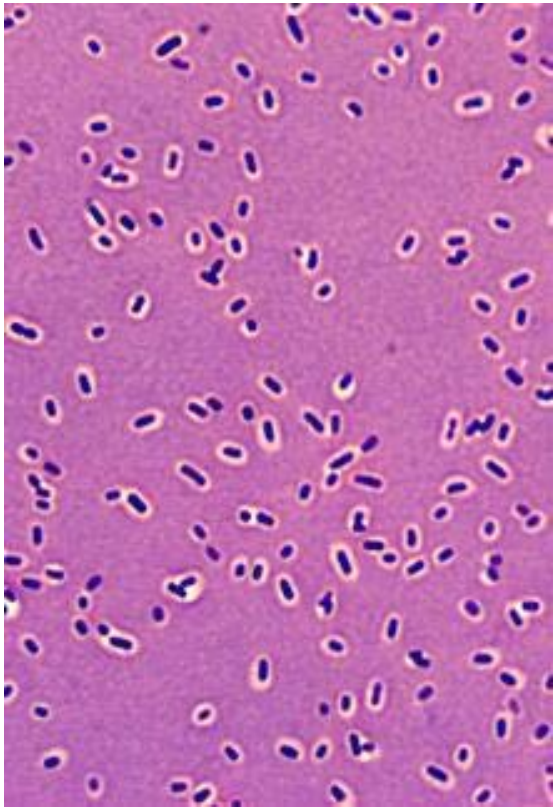
- Causes frequent infections within hospitals.
- Fourth and fifth most common cause of pneumonia and bacteremia, respectively, in intensive care patients



National Institute of Allergy and Infectious Diseases
Figure 1. *Klebsiella pneumoniae*

“Super Bug”

- Drug-resistant
- Produces carbapenemase, gains resistance to the major antibiotic class of carbapenems
- Fatal outcome in nearly half of infection cases



National Institutes of Health
Figure 2. *Klebsiella pneumoniae*

- Experimental drug development:
  - Expensive
  - Time-consuming
  - Sometimes impossible

- Virtual screening of drugs
  - Fast
  - Cheap
  - Effective
  - Flexible - able to make modifications

Project Approach

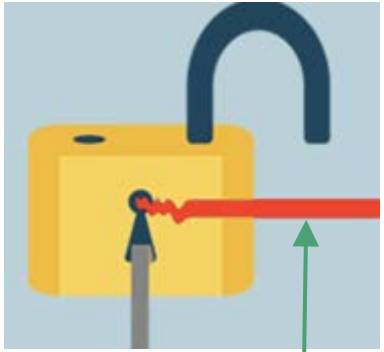
Virtual screening with drug library

Introduce biosynthetic modifications

Test performance of biosynthetic molecules

Project Approach - an analogy

MORF



Drug

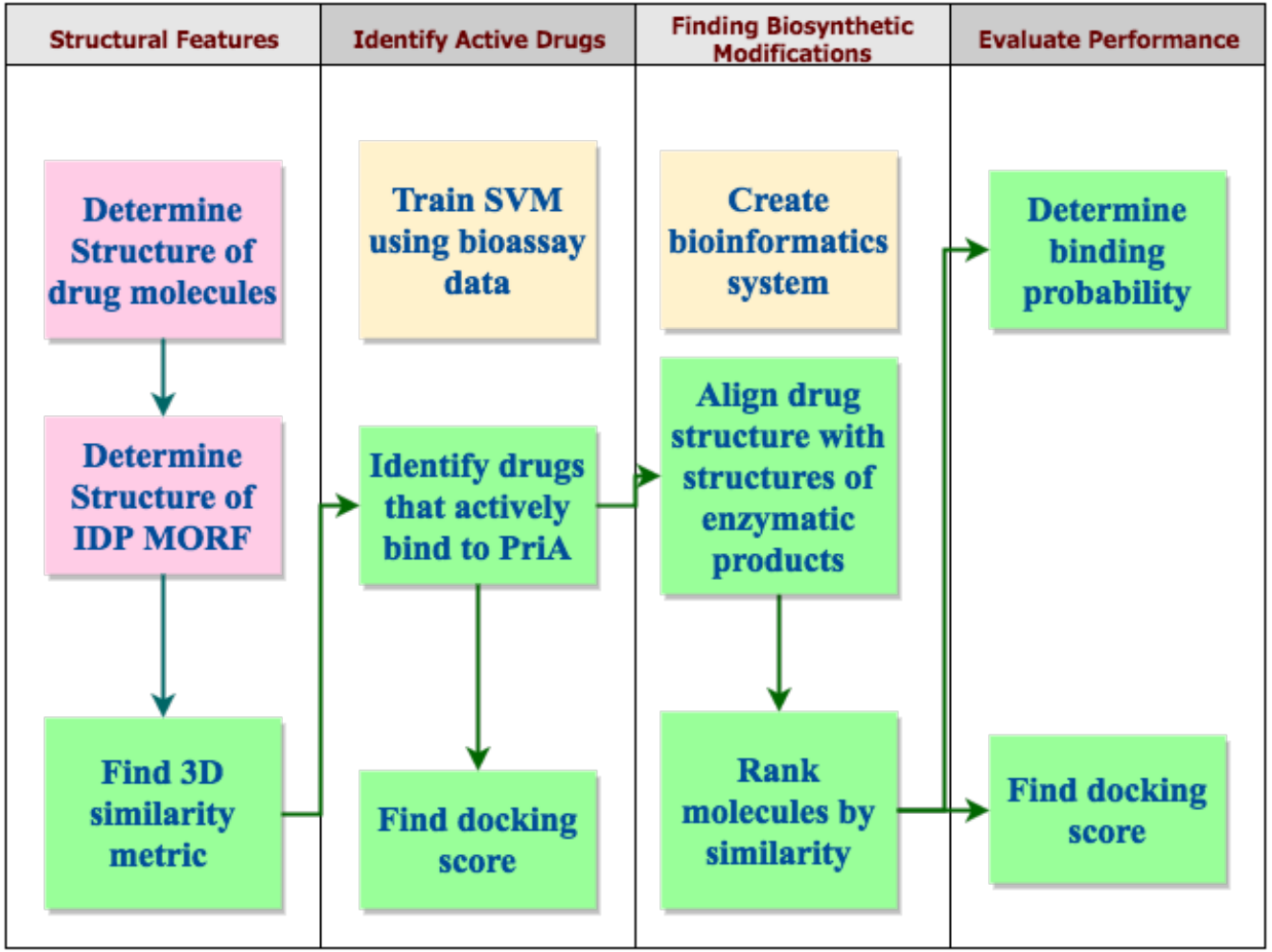
Biosynthetic molecule

Protein Target - PriA

- Catalyzes cellular “replication restart” reactions.
- Aids the completion of replication and cell growth.
- Interacts with the C-terminal peptide of single-stranded DNA-binding proteins (SSBs).

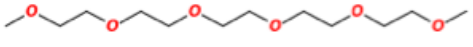
RCSB Protein Data Bank
Figure 3. *Klebsiella pneumoniae* PriA bound to SSB

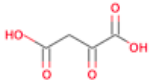
Methods


Structural Features
Identify Active Drugs
Finding Biosynthetic Modifications
Evaluate Performance
Determine Structure of drug molecules
Determine Structure of IDP MORF
Find 3D similarity metric
Train SVM using bioassay data
Identify drugs that actively bind to PriA
Find docking score
Create bioinformatics system
Align drug structure with structures of enzymatic products
Rank molecules by similarity
Determine binding probability
Find docking score

Biosynthetic Modifications

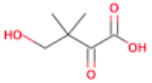
Generate molecular features for ligand recognition that are more likely to bind to novel targets





ID:300036 formula: C4H4O5
weight: 128.039

ID: C00424 formula: C3H6O2
weight: 68.031



ID: C00966 formula: C6H10O4
weight:136.062

The structure of ZINC04530388 → Its top three biosynthetic modifications

Initial Identification

-6.5 kcal/mol is considered a possible drug target
-9.0 kcal/mol is considered an ideal drug

Drug ID	Binding Probability	Docking Score
ZINC58632138	0.936600803	-8.4
ZINC96006023	0.926566162	-8
ZINC96006130	0.923714254	-6.3
ZINC53683423	0.919408977	-6.8
ZINC38664731	0.919357363	-8.4

Results

-6.5 kcal/mol is considered a possible drug target
-9.0 kcal/mol is considered an ideal drug

Original Drug	Docking Score	Modified Molecule	Docking Score
ZINC58632138	-8.4	00001	-10.4
ZINC38664731	-8.4	00117	-10.1
ZINC53683423	-6.8	40359	-10.1
ZINC96006023	-8	20135	-11.8
		60001	-11.4

Discussion

- Improvements for existing drug molecules that target *Klebsiella pneumoniae* are found by looking at molecules with similar molecular structures.
- Computer simulations show that drug performance is greatly increased by such modifications.

Future Directions

- Blocking by allosteric hindrance
- Analyzing well-performing molecules for common structure
- Constructing new drugs using fragment-based design
- Apply this method to other organisms
- Expand drug database and bioinformatics database

Acknowledgments

- MIT PRIMES
- Chief Research Advisor Pavel Etingof
- Program Director Slava Gerovitch
- Computer Science Section Faculty Coordinator Srini Devadas
- Dr. Gil Alterovitz
- University of Science and Technology of China
  - Especially Shilin Zhu and Yicheng Fei

References

1. B. Bhattacharyya, N. P. George, T. M. Thurmes, R. Zhou, N. Jani, S. R. Wessel, S. J. Sandler, T. Ha, and J. L. Keck. Structural mechanisms of PriA-mediated DNA replication restart. *Proc Natl Acad Sci U S A*, 111(4):1373–8, 2014.

2. H. W. Boucher, G. H. Talbot, J. S. Bradley, J. E. Edwards, D. Gilbert, L. B. Rice, M. Scheld, B. Spellberg, and J. Bartlett. Bad bugs, no drugs: no eskape! an update from the infectious diseases society of america. *Clin Infect Dis*, 48(1):1–12, 2009.

3. E. Byvatov and G. Schneider. Support vector machine applications in bioinformatics. *Appl Bioinformatics*, 2(2):67–77, 2003.

4. J. Carlet, V. Jarlier, S. Harbarth, A. Voss, H. Goossens, D. Pittet, and Forum Participants of the 3rd World Healthcare-Associated Infections. Ready for a world without antibiotics? the pensieres antibiotic resistance call to action. *Antimicrob Resist Infect Control*, 1(1):11, 2012.

5. F. M. Disfani, W. L. Hsu, M. J. Mizianty, C. J. Oldfield, B. Xue, A. K. Dunker, V. N. Uversky, and L. Kurgan. MoRFpred, a computational tool for sequence-based prediction and characterization of short disorder-to-order transitioning binding regions in proteins. *Bioinformatics*, 28(12):i75–83, 2012.

6. D. R. Guay. Contemporary management of uncomplicated urinary tract infections. *Drugs*, 68(9):1169–205, 2008.

7. C. Haynes, C. J. Oldfield, F. Ji, N. Klitgord, M. E. Cusick, P. Radivojac, V. N. Uversky, M. Vidal, and L. M. Iakoucheva. Intrinsic disorder is a common feature of hub proteins from four eukaryotic interactomes. *PLoS Comput Biol*, 2(8):e100, 2006.

8. W. L. Hsu, C. J. Oldfield, B. Xue, J. Meng, F. Huang, P. Romero, V. N. Uversky, and A. K. Dunker. Exploring the binding diversity of intrinsically disordered proteins involved in one-to-many binding. *Protein Sci*, 22(3):258–73, 2013.

9. C. R. Hutchinson. Combinatorial biosynthesis for new drug discovery. *Curr Opin Microbiol*, 1(3):319–29, 1998.

10. A. Y. Peleg and D. C. Hooper. Hospital-acquired infections due to gram-negative bacteria. *N Engl J Med*, 362(19):1804–13, 2010.

11. A. Stucki, F. Acosta, M. Cottagnoud, and P. Cottagnoud. Efficacy of ceftaroline fosamil against escherichia coli and klebsiella pneumoniae strains in a rabbit meningitis model. *Antimicrob Agents Chemother*, 57(12):5808–10, 2013.

12. T. Oleg and A.J. Olson. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comp Chem* 31(2): 455-461, 2010.

13. S. A. Weisenberg, D. J. Morgan, R. Espinal-Witter, and D. H. Larone. Clinical outcomes of patients with klebsiella pneumoniae carbapenemase-producing k. pneumoniae after treatment with imipenem or meropenem. *Diagn Microbiol Infect Dis*, 64(2):233–5, 2009.

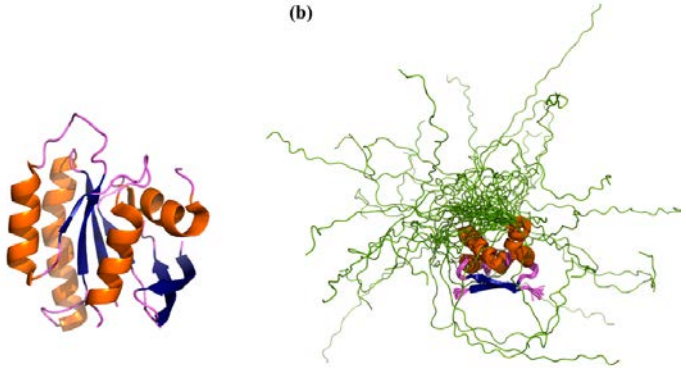
14. P. E. Wright and H. J. Dyson. Linking folding and binding. *Curr Opin Struct Biol*, 19(1):31–8, 2009.

15. Vikramaditya Ganapati Yadav. Biosynthetic engineering for the assembly of better drugs. *MIT PhD Thesis*, 2013.

16. E. Freire. A Thermodynamic Approach to the Affinity Optimization of Drug Candidates. *Chem Biol Drug Des*, 2009.

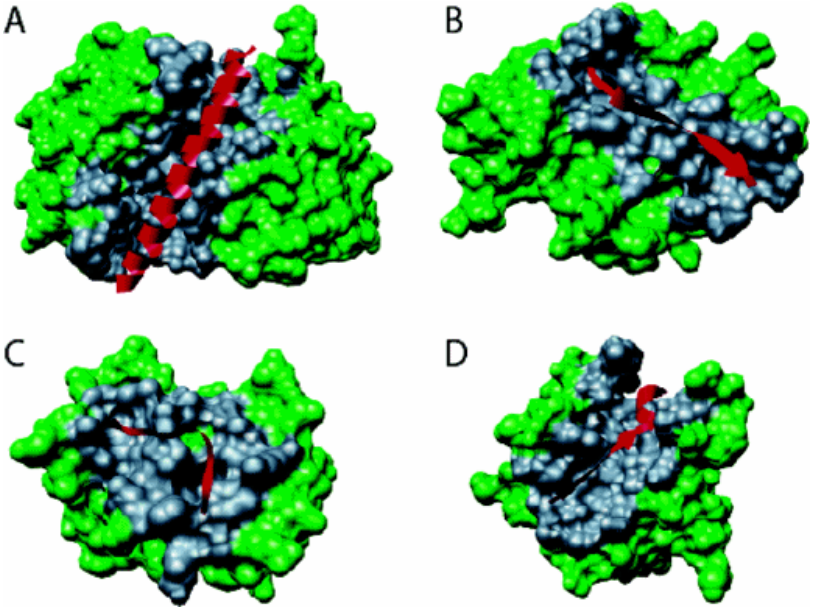
Intrinsically Disordered Proteins

- Lack a fixed or ordered 3D structure
- Flexible, easy to bind to
- Have close relationships with human diseases such as tumor, Parkinson disease, Alzheimer disease, diabetes, etc



MDPI
Varied degree of order in proteins. (a) Has well defined three-dimensional coordinates (b) protein with both an ordered region and an IDR

Molecular Recognition Features (MoRFs)



UC Davis
Examples of molecular recognition features (MoRFs)

- Small, intrinsically disordered region of a protein
- Bind to partners, serves as an initial step in molecular recognition