# Molecular modeling of metabolic enzymes from pathogenic bacteria

We are working with [Oscar Juarez from the biology department](https://juarezlab.wixsite.com/research), performing molecular modeling to characterize metabolic enzymes in pathogenic bacteria. Most of our collaborative work has been on the ion pump NQR. In Tuz et. al. [1], we performed molecular docking of ubiquinone to the entire complex and predicted the catalytic binding site. The predicted site was corroborated by site-directed mutagenesis and modified biochemical activity. We then performed molecular docking to mutants of subunit D and obtained results consistent measured activity [2]. We have also performed homology modeling and molecular dynamics simulations to help identify a critical pair of residues which are swapped between the homologs from V. Cholera and P. Aeruginosa [3]. When the residues were mutated in the *V. cholera* homolog, it exhibited the predicted resistance to the natural antibiotic HQNO. Our groups have also collaborated on the flavin transferase ApbE, which is involved in the biosynthesis of NQR [4]. We performed pKa calculations to corroborate the proposed enzymatic mechanism of the enzyme. Our groups are funded by a NIH grant that includes the discovery of succinate dehydrogenase (another metabolic enzyme) inhibitors through novel methods for binding free energy calculations.

## Related references

[1] K. Tuz *et al.*, “Identification of the Catalytic Ubiquinone-binding Site of Vibrio cholerae Sodium-dependent NADH Dehydrogenase,” *Journal of Biological Chemistry*, vol. 292, no. 7, pp. 3039–3048, Feb. 2017, doi: 10.1074/jbc.M116.770982.

[2] D. A. Raba *et al.*, “Role of subunit D in the ubiquinone binding site of Vibrio cholerae NQR: pocket flexibility and inhibitor resistance,” *ACS Omega*, vol. 4, no. 21, pp. 19324–19331, 2019, doi: 10.1021/acsomega.9b02707.

[3] D. A. Raba *et al.*, “Characterization of the Pseudomonas aeruginosa NQR Complex, a Bacterial Proton Pump with Roles in Autopoisoning Resistance,” *Journal of Biological Chemistry*, vol. 293, pp. 15664–15677, 2018, doi: 10.1074/jbc.RA118.003194.

[4] X. Fang *et al.*, “Conserved residue His-257 of Vibrio cholerae flavin transferase ApbE plays a critical role in substrate binding and catalysis,” *Journal of Biological Chemistry*, vol. 294, pp. 13800–13810, 2019, doi: 10.1074/jbc.RA119.008261.