Cracking the Code: Predicting Small Molecule Binding to a Cryptic, Dynamic Protein Pocket

Brittany S. Morgan, *John V. O'Connor Assistant Professor of Cancer Drug Discovery, Department of Chemistry and Biochemistry, Notre Dame University*

The human proteome contains over 20,000 proteins that when mutated or dysregulated, often lead to disease. Currently, small molecule drugs have been discovered for less than 5% of our proteome, and it is proposed that targeting the other 95% of proteins will uncover novel treatments and cellular biology. Herein, I will discuss my work toward targeting undruggable proteins, particularly proteins with dynamic and/or disordered structures. These proteins do not conform to the classic lock-and-key model, often lack traditional binding pockets for small molecules, yet are critically important for cellular function and disease. By utilizing covalent ligands, cryptic and/or hidden binding pockets were discovered in a dynamic protein, Med25, that is important for gene transcription. Computational models were built that uncovered and predicted ligand features critical for binding. One of those features, ligand shape, was key for regulating protein activity and structure. The strategy of using covalent ligands to target dynamic and/or disordered proteins is expected to vastly expand our druggable proteome and revolutionize our understanding of function, structure, and disease. In addition to research, I will also talk about my pathway to science, including my journey as a first-generation college student, first-generation career woman, and student from rural, small-town America.

Molecular Recognition Interactions for Proposed Fragment 22 Binding Site