Ubiquitination is a highly conserved post-translational modification that is critical to achieving normal cellular functions, as well as the overall maintenance of protein homeostasis. E3 ubiquitin ligases catalyze protein ubiquitination by facilitating the transfer and subsequent covalent attachment of ubiquitin to a variety of target substrates. This process is essential for normal cellular functions, making E3s attractive therapeutic targets. Homologous to the E6AP C terminus (HECT) subfamily of E3 ubiquitin ligases are involved in many important biological processes such as cancer development, immune function, hypertension among others. I am particularly interested in the two Smurf (Smad ubiquitin regulator factor) proteins (Smurf1 and Smurf2), which are deeply involved in crucial cellular processes such as DNA damage response, gene expression, chromatin organization and cell migration and invasion. Not surprisingly, both Smurf1 and Smurf2 have been implicated in the progression of multiple human cancer types. Therefore, developing synthetic modulators of Smurf proteins is of critical importance to better understand their roles in human health and disease.

In the past few years, a combinatorial structure-based protein engineering strategy has been used to produce ubiquitin variants (UbVs) to manipulate enzymes in the ubiquitination pathway. In particular, synthetic UbV inhibitors were engineered for several HECT E3 ligases. In this project, I will identify potent and specific UbVs to inhibit Smurf proteins, with a main focus on Smurf2. This research will lead to the better understanding of Smurf proteins and potentially lead to the development of small-molecule inhibitors and therapeutics targeting Smurf proteins.