Project 3. Studies of specific inhibition mechanisms of kinase isoforms and structure-guided discovery of selective kinase inhibitors

Protein kinases are essential components of cellular function and development. Misregulation of kinases causes inappropriate cellular responses, which ultimately result in disease. Usually, constitutively activated kinases are involved in human cancer, and inhibition of hyperactive protein kinases has been a popular approach for the development of cancer-targeted therapies. Toxicity issues in clinical studies are mainly related to off-target effects by pan-kinase drugs. However, achieving specific inhibition of an individual kinase is a challenging task due to the highly conserved ATP binding site across the kinome (>500 kinases in humans). In addition, pan-kinase inhibitors have limited value in biomedical research, where their use can cause confusion. Consequently, few isoform specific kinase inhibitors are currently available. These compounds were discovered in a serendipitous manner by screening large chemical libraries, rather than a rational design approach.

We previously developed highly specific CK1ε inhibitors via computer-aided drug design approaches, starting from dual CK1δ/ε inhibitors. This achievement inspired my conception of the following fundamental questions:

- *Why do the kinase isoforms possessing 97% sequence identity respond differently to specific inhibitors?*
- *Can we establish theoretical/experimental models to elucidate specific inhibition mechanism(s) of the kinase isoforms?*
- *Can the lessons learned by studying CK1δ and CK1ε be applied to other kinase isoforms?*

Thus, the CK1ε-specific and dual inhibitors will be utilized as chemical probes to elucidate specific inhibition mechanisms of CK1δ/CK1ε isoforms via chemical biology, structural biology, and computational approaches. Later, the established theoretical models will be applied to other kinases to discover other specific kinase inhibitors such as CK1α, CK1δ, CK1γ, etc.

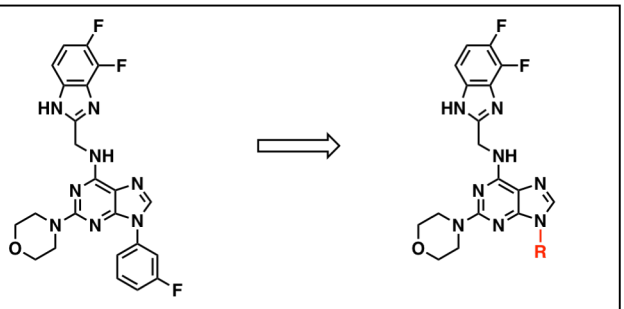

Figure 1. Structure-guided design and development of highly potent and selective CK1ε inhibitors