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Applications of biophysical methods in small-molecule modulators targeting protein function

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Chapter 8

Summary

Structure-based drug design method is a powerful method for discovering new ligands against important targets. After the structure of that target determined, new ligand can be designed from chemical principles or chosen from a subset of small molecules that score well in *in silico* docking. After a preliminary assessment of bioavailability, candidates continue into an iterative process of structure determination and re-evaluation for optimization.

In Chapter 2, the review was written as summary of IL17A commercial inhibitors. In 2016, researchers from Pizer determinated three small molecule including two macrocycles as IL17A/IL17RA inhibitors. In deposited structures, the bound HIP at the widened N-terminus was implied to contribute more possibilities for ligand binding between two IL17A dimers. However, it is important to note how the IL-17A dimer in cells adopt such distinct conformations? Even so, they provided key advances in designing novel class ligand in the central cavity. Based on their contributions, we took use of complex structure IL17A/63Q to design a basic scaffold in the Chapter 5, and screened MD01 and MD09 compound as leads to optimize further MD compounds and accumulate information and experience to discovery novel binders. In Chapter 6, we described 1 lead compound F2 with crystal structure with IL17A, the efforts to design and screen provide key information for us to successfully discovery a new series compound implied binding

affinity at nano molar and inhibition efficiency from IL17A signal pathway. Until now, two structures of them have been determined (F2 and F37). It is good starting to investigate anti-IL17A small molecule antagonist.

Chapter 3, bCAII was used as a model system to develop *in vitro* labeling approaches. We successfully got apo bCAII crytal diffracted to 1.8Å. Based on the apo structure, 7 ligands were used in X-ray crystallography studies to understand how the probes binding and labeling.This study is an example in combination of chemical biology methods, X-ray crystallography and protein tandem mass spectrometry to illustrate insight into the protein–probe interactions.

In Chapter 4, we obtained the structure of the *Pf* pdxk complex with AMP-PNP and PL. In this study we found a (XMXH)m motif region within *Pf* pdxk without affecting structural integrity. It was proposed to play an important role in malaria cell cycle. In addition, we took used of *in silico* modeling to speculate the mechanism that *Pf* Pdxk selectively phohspohrylated PT3, PT5 and PHME into potential active anti-malaria drug. Although *in silico* modeling to predict the binding mode of potential ligand cannot provide a solid and accuracy results, they provides valuable possibility to guide experimental validation in future studies.

In Chapter 7, we made use of Microscale thermophoresis (MST) to determinate the potential binding affinity of 3-FL, LNnT, and LDFT with His-TNFR1 receptor. From the results, only LNnT was observed to show a ligand-dependent binding effect of LNnT with His-TNFR1 of a *Kd* around 900nM. It proposed LNnT might bind directly to TNFR1 in structure-function relationship to perform its anti-inflammatory effect .

In all, the application of biophysical methods plays very crucial roles in small-molecule modulators targeting protein function research.

Besides, to optimize a promising hit into a potential lead molecule, the determination of structure is very critical. X-ray crystallography is amenable to the realm of FBDD. However, an area in which structural biology has been struggling for many years is integral membrane proteins (IMP). Due to their large hydrophobic regions embedded in the membrane, their structural and functional integrity is often membrane-dependent. The development in electron microscopy allows the determination of the structure of proteins

and proteins complexes at near-atomic resolution by Cryo-EM. With these techniques, the conformation of the protein, especially IMP is against not constrained by growing crystals. It may provide a more natural way to obtain insight into the conformation of a drug target as part of a more physiological protein complex, thus offer crucial information complementary to the inhibitor design efforts on isolated protein targets or protein domains.

The first Cryo-EM structure visualizing bound small-molecule ligands have already been reported and include ribosome structures with bound antibiotics and the human 20S proteasome structure with a covalently bound substrate analogue. Together, the combination of X-ray crystallography and Cryo-EM will become more powerful methods in structure-based drug design. The step forward to structure-based drug design will not stop.