Discovery of Active Compounds for Ion Channels Using Rational Design Method

SPEAKER: Huaiyu Yang, East China Normal University
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VENUE: Room 385, Geography Building, ECNU Zhongbei Campus

ABSTRACT OF THE TALK
We first studied interactions of lipid PIP2 with voltage-gated Kv channel KCNQ2 through MD simulation. This work discovered a two-site model of binding between PIP2 and KCNQ2. And then based on the MD conformations, we identified a dynamic pocket in KCNQ2 that might be the binding site of a small molecule activator. Subsequent targeted mutations coupled with functional assays confirmed this binding site. Then a structure-based virtual screening assay targeting the defined ligand binding site identified nine activators with new chemotypes, and in vivo experiments showed three ligands exhibit significant anti-epilepsy activity. This work paved way for future optimization of the small molecule activator and provides a novel concept of molecular targeting of dynamic pockets that may not exist in static crystal structures. Recently, our study on K2P channels further suggested that drug discovery for other ion channels could also pay attention to dynamic pockets.

BIOGRAPHY
Professor Yang got his Ph.D. degree from Shanghai Institute of Materia Medica in 2008. He joined ECNU last year and established a group which is mainly engaged in the chemical biology study on the structure-function relationship of transmembrane-protein drug targets. Based on the understanding of protein dynamics, he has discovered novel active small molecules using rational design methods for several ion channels, such as KCNQ2, KCNQ4, TREK1, TASK3, TRAAK, TRPV2 and TRPV6 channels. His group is developing the compounds into medicines for treating diseases of nervous systems.