

Discovery of novel small-molecules and mechanism study via chemical biology and genetic approach

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Small molecule modulators regulating individual protein function have enabled a new possibility for elucidating multifaceted biological network and created effective connection between academic and clinical research. Phenotypic screening has emerged as a promising approach to discover novel bioactive small-molecule modulators and to bring out new molecular entities in drug discovery. However, efficiency of phenotypic screening generates the limitation on further study or clinical application of the molecules without complete validation of their therapeutic target. Therefore, target identification and elucidating mechanism-of-action for bioactive compounds are indispensable factor. Herein, we discuss the establishment of systematic chemical biology platform and genome-wide genetic screening including 1) development of chemical tools for monitoring specific biological event, 2) application to high-throughput screening system, 3) identification of interesting small-molecule modulators, 4) target identification, and 5) discovery new signaling pathway for therapeutic effect. Based on the series of studies, we successfully discovered various bioactive small molecules and a pair of known drug for synergy effect — a selective FLT3 kinase inhibitor for anti-cancer agent, autophagy modulators, HMGB-binding small molecule for preventing neuroinflammation, and new pathway for next generation of cancer immunotherapy.

(1) *Nat. Chem. Biol.* **2014** 10, 1055 (2) *Chem. Sci.* **2013** 4, 3282 (3) *Med. Chem. Comm.* **2013** 4, 228
(4) *Chem. Commun.* **2012** 48, 2331