项目摘要

中文摘要(500字以内)：

组蛋白赖氨酸特异性去甲基化酶LSD1在肺癌组织中高表达且与肿瘤增殖、侵袭与转移及不良预后密切相关，小分子抑制剂或RNAi介导的LSD1抑制或低表达可抑制肿瘤细胞增殖、转移和侵袭。不可逆LSD1抑制剂ORY-1001、GSK-2879552和INCB059872已进入临床试验用于治疗白血病和小细胞肺癌，而可逆LSD1抑制剂尚未进入临床阶段的研发。在前期工作基础之上，本项目拟开展：（1）、利用高通量虚拟筛选技术并结合基于结构的药物设计等方法设计新型肺癌靶向的LSD1可逆抑制剂，并通过生物电子等排和骨架跃迁等方法构建具有结构多样性和复杂性的小分子化合物库；（2）、基于PROTACs策略设计新型LSD1降解剂，并探索其用于肺癌治疗的可能性。通过分子、细胞和动物水平的抗肿瘤活性毒性评价和机制研究，期望获得2-3个高效高选择性的候选化合物，为今后探索以LSD1为靶点的抗肿瘤药物设计提供理论基础。

关键词：肺癌；组蛋白赖氨酸特异性去甲基化酶1；LSD1抑制剂；蛋白降解剂；抗肿瘤活性

Abstract(limited to 4000 words)：

Histone lysine specific demethylase 1 (LSD1) is overexpressed in lung tissues and closely related with tumor proliferation, evasion, migration, and poor prognosis, inactivation or down-regulation of LSD1 by small molecules or RNAi leads to inhibition of proliferation, migration and evasion. Three irreversible LSD1 inhibitors, namely ORY-1001, GSK-2879552, and INCB059872, have advanced into clinical trials for the treatment of AML and SCLC, while no reversible LSD1 inhibitors are currently investigated in clinical trials. Following our previous work on LSD1, we intend to carry out the following work: (1) Design of new LSD1 inhibitors employing the high throughput virtual screening and structure-based drug design strategies, and then to establish the small-molecule library of LSD1 with structural diversity and complexity based on the bioisosteric replacement and scaffold hopping methods; (2). We also plan to design novel LSD1 protein degraders based on the PROTACs strategy and to explore the feasibility of LSD1 degraders for the treatment of lung cancer. In this project, we are expecting to obtain 2-3 highly potent and selective small-molecule compounds targeting LSD1 through multi-level activity evaluation, and mechanistic investigations, hoping to provide evidence for the design of novel anticancer drugs targeting LSD1.

Keywords: Lung Cancer; Lysine Specific Demethylase 1; LSD1 Inhibitors; Protein Degraders; Anticancer Activity