세미나 초록

성명	김필호
소속	한국화학연구원
발표 주제	Journey to discover BTK degraders for the treatment of hematologic cancers
발표 내용	Inhibition of B-cell receptor (BCR) signaling pathways could be considered well-validated strategies for the treatment of chronic lymphocytic lymphoma (CLL), mantle cell lymphoma (MCL), and other B-cell related cancers. In this context, Bruton's Tyrosine Kinase (BTK) plays an essential role in BCR pathway and its activation leads to growth, survival, and proliferation of leukemic B-cells. Hence, targeting BTK has proven to be a practical way for the treatment of hematological cancers. Ibrutinib, the first irreversible BTK inhibitor approved in 1993, deactivates BTK by binding covalently to the C481 present in the ATP binding site of BTK, providing a breakthrough therapy for the treatment of leukemia and lymphomas. Along with ibrutinib, FDA has approved acalabrutinib and zanubrutinib in 2017 and 2019, respectively, as irreversible BTK inhibitors for the treatment of MCL and CLL. However, due to the C481 mutations in the binding site of BTK, the patients treated with irreversible BTK inhibitors acquire inevitable resistance leading to tumor progression. Thus, novel approaches, such as reversible inhibitors or PROteolysis-TArgeting Chimeras (PROTACs), would be ungently required to overcome this issue. Contrary to the small molecule inhibitors, PROTACs are heterobifunctional molecules, which degrade the target protein by hijacking natural ubiquitin proteasome system (UPS). A typical PROTAC compound is composed of a target protein binder, E3 ligase binder, and a linker that connects both of the binders. In 2019, two clinical trials were launched by Arvinas utilizing protein degraders, ARV-110 and ARV 471. While ARV-110 is targeting androgen receptor for the treatment of prostate cancer, ARV-471 is targeting estrogen receptor for breast cancer. Currently, clinical trials are underway with two BTK degraders, NX-2127 and BGB-16673 by Nurix and Beigene, respectively. While our team has designed and synthesized novel BTK degraders utilizing KRICT-owned BTK inhibitors, Ubix therapeutics has performed in vitro and in vivo bioassays. One of the most active compounds, TD-1082, showed in vitro activities far better than those of a reported BTK degrader, MT-802. TD-1082 turned out to have superior pharmacokinetics and in vivo efficacy in murine xenograft models, compared with ibrutinib and other reported BTK degraders. In this lecture, our journey to discover BTK small molecules and TD-1082 will be presented.