28AB-ISMS24 **Hybrid Molecules of β-Carboline and Bis(hydroxymethyl)pyrrole with Topoisomerase I/II Inhibitory and DNA Cross-linking Activities Are Potent Anticancer Agents**

○Te-Chang LEE[1], Sue-Ming CHANG[1], Ming-Hsi WU[1], Chi-Wei CHEN[1], Tsann-Long SU[1]
[1]Institute of Biomedical Sciences, Academia Sinica

Hybrid molecules formed by integration of two drug pharmacophores into a single molecule may generate new compounds with multiple modes of action. Accordingly, we designed and synthesized a series of hybrid molecules consisted of a β-carboline group and a bis(hydroxymethyl)pyrrole fragment. The β-carboline analogues were reported to function as topoisomerase (Topo) I/II inhibitor and bis(hydroxymethyl)pyrrole moieties were able induce DNA cross-links (ICLs). We have successfully produced a family of structural isomerism derivatives, indolizino[6,7-*b*]indoles and indolizino[8,7-*b*]indoles. In our previous report[1], we have shown that indolizino[6,7-*b*]indole derivatives possessed multiple modes of action, including induction of DNA interstrand cross-links (ICLs), inhibition of Topo I/II, and cell-cycle arrest at the S-phase. In addition, they potently suppressed the growth of human colon and lung cancer cells in xenograft models. Recently, we further demonstrated that one of indolizino[6,7-*b*]indole hybrids, named as BO-1978, significantly suppressed the growth of several EGFR wild type and mutant human non-small-cell lung carcinoma (NSCLC) tumors in xenograft tumor and orthotopic lung tumor models. The combination of BO-1978 with gefitinib further suppressed the growth of EGFR mutant NSCLC cells in xenograft tumor and orthotopic lung tumor models. At the dose used for animal study, BO-1978 did not cause significant toxicity in mice, implicating that BO-1978 is a potential therapeutic agent for treatment of NSCLC. Similarly, the indolizino[8,7-*b*]indole isomerism family were also revealed to display multiple functions comprising induction of DNA ICLs and inhibition of Topo I/II. These molecules exhibited significant cytotoxicity against the cell growth of a variety of human tumor cell lines in vitro. Our present studies suggest that hybrid molecules with topoisomerase inhibitory and DNA ICL activities may serve as potent antitumor agents and warrant our further development.

Reference

1 Chaniyara R, Tala S, Chen CW, Zang X, Kakadiya R, Lin LF *et al*. Novel antitumor indolizino[6,7-b]indoles with multiple modes of action: DNA cross-linking and topoisomerase I and II inhibition. *J. Med. Chem.* **2013**, *56*, 1544-1563.