27O-ISMS10 Controlled Release of Anticancer Drugs by LSD1 Inhibition

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Lysine-specific demethylase 1 (LSD1) is overexpressed in cancer cells and associated with cancer cell growth.[1] Thus, LSD1 is an attractive target for cancer therapy. To date, a number of LSD1 inhibitors have been developed.[1] Most of them are *trans*-2-phenylcyclopropylamine (PCPA)-based irreversible inhibitors that can react with FAD in the active site of LSD1. In the course of LSD1 inhibition by PCPA, an ammonia molecule would be released through hydrolysis of an imine intermediate.[2] Based on these findings, we proposed PCPA-drug conjugates (PDCs) as drug delivery molecules (**Figure 1**). PDCs would release a drug by LSD1 inhibition in cancer cells where LSD1 is overexpressed, while PDCs would not release in normal cells where LSD1 is hardly expressed (**Figure 1**). Previously, we reported PCPA-tamoxifen conjugates as prototypes of PDCs to show the utility of controlled release of anticancer drugs by LSD1 inhibition.[3] In order to confirm the generality of PDCs, we are studying on PDCs releasing another drug such as a histone deacetylase inhibitor (HDACi) used clinically for cancer therapy. In this symposium, we report the design, synthesis and biological evaluation of the PCPA-HDACi conjugates.

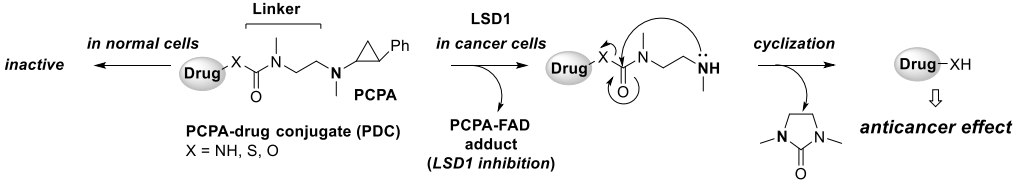

Figure 1. Concept of controlled release of anticancer drugs by LSD1 inhibition

(References)
(1) Suzuki, T.; Miyata, N. *J. Med. Chem.* **2011**, *54*, 8236–8250; (2) Yang, M. *et al. Biochemistry* **2007**, *46*, 8058–8065; (3) Ota, Y. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 16115–16118.