Fabrication of Novel Nano-Prodrugs that Release Drugs with High Efficiency in Cancer Cells

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In recent years, drug nanoparticles called nano-prodrugs (NPDs), which are composed only prodrug molecules, have been proposed and fabricated. The NPDs have a higher drug loading ratio than conventional nanodrugs using carrier, and there are many reports on various NPDs, which composed of substituents-conjugated SN-38.[1,2] Most of these SN-38 derivative NPDs exhibits relatively higher pharmacological activity *in vitro* compared to irinotecan, a clinically used water-soluble prodrug of SN-38. However, it was concerned that those SN-38 derivative NPDs would be partially dissociated in blood through esterase-induced metabolism of the ester bond that connects SN-38 to the substituents. Therefore, it is necessary to develop novel NPDs that release SN-38 only after accumulated in tumor tissues. In this study, we focused on glutathione (GSH) as a cancer cell-specific trigger. GSH is a tripeptide that reduce disulfide (S-S) bond and presents at high concentration in cancer cells (ca. 10 mM). It was hypothesized that the prodrugs with S-S bond in their molecular design were able to release a drug only inside cancer cells.

SN-38 prodrugs with S-S bond (SNC4DC) were synthesized (Fig. 1 (a)). Subsequently, the obtained SN-38 prodrugs were fabricated into novel NPDs and followed by evaluation of their drug release behavior and *in vivo* anticancer activities. It was showed that SNC4DC was released SN-38 monomer under S-S bond reducing conditions by intramolecular cyclization. As shown in Figure 1 (b), the SNC4DC NPDs- administered group showed the higher activity compared to the irinotecan-administered groups.

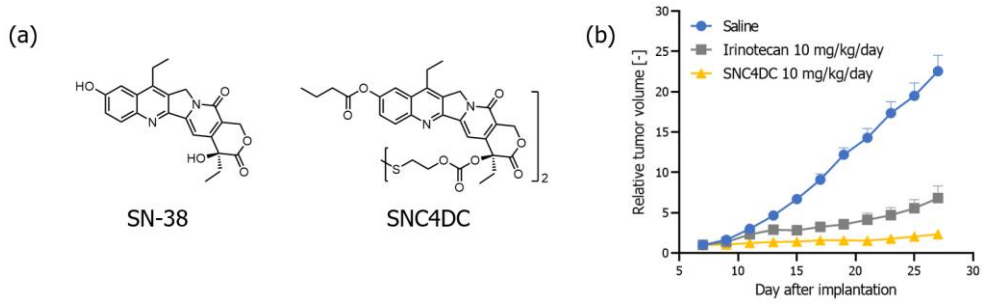

Figure 1. (a) Chemical structure of SN-38 and SN-38 prodrug, (b) *In vivo* experiment of SNC4DC NPDs. The relative tumor volume was determined as V/V_0 (V_0 was the initial tumor volume before treatment).

1) Y. Koseki *et al*., *Bull*. *Chem*. *Soc*. *Jpn*. **2019**, *92*, 1305–1313.
2) K. Tanita *et al*., *Chem*. *Lett*. **2020**, *49*, 222–224.