Glycosidic switch liposomes

Yu-Lin Leu[1]; Chun-Hung Lin[2]; Steve Roffler[3]

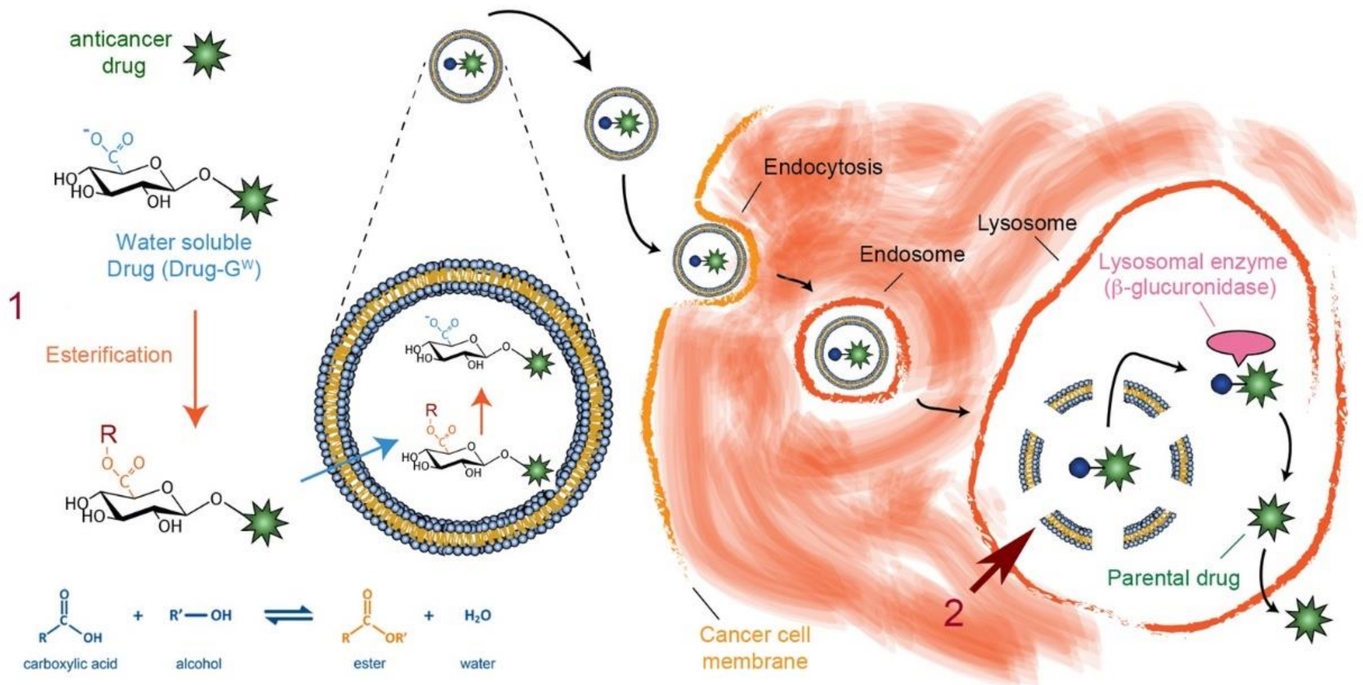
1. Department of Pharmacy, Chia Nan University,
2. Institute of Biological Chemistry, Academia Sinica,
3. Institute of Biomedical Sciences, Academia Sinica

OBJECTIVE

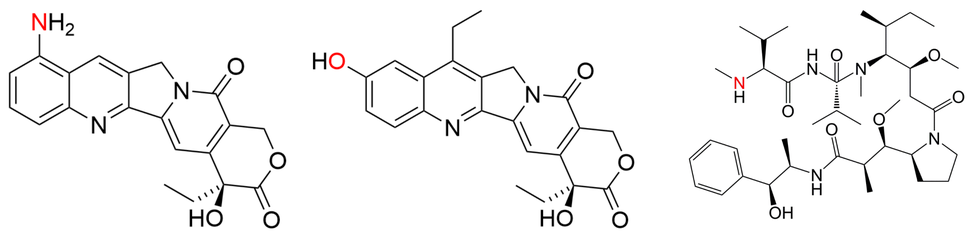
Develop potent liposomal drugs for the therapy of patients suffering from pancreatic cancer

ABSTRACT

Liposomes are an established nanotechnology for cancer therapy. Although liposomal nanocarriers are increasingly impacting the clinical treatment of cancers, progress is limited by the lack of a general platform to load and retain anticancer agents in liposomes. We overcome this limitation by chemically incorporating a “glycosidic switch” into anticancer drugs. The glycosidic switch can be controllably interconverted between a lipid-soluble ester form for loading and a water-soluble glucuronide form for stable drug retention in the aqueous core to create glycosidic switch liposomes (GSL, **Fig. 1**). Our first GSL which encapsulated with 9ACG, that displays promising anti-tumor efficacy compared to the clinical-used drugs for pancreatic cancer, gemcitabine and Onivyde® (Liposomal CPT-11 injection) (**Fig. 2**). SN-38 is an attractive candidate for glycosidic switch strategy, that is an activated metabolite of CPT-11 in the treatment of various malignancies, that also be glucuronidated via an extensive conjugation with D-glucuronic acid through the UDP-glucuronosyltransferase 1A1/9. However, the synthesis of this natural SN-38G is challenging, regardless of chemical route or animal, the production yield is lower than 5%. Currently, we developed a new synthesizing strategy for SN-38G with a superior yield of over 70%. Moreover, we obtained liposomal SN-38G through the GSL strategy with high loading efficiency (80%) and nearly 100% retention stability(**Table. 1**). Besides camptothecin derivatives, we also developed MMAE, an auristatin analog that displays higher potency, to seek an appropriate candidate for GSL. The V.5 shows promising loading efficiency (38%) and 98% retention stability(**Fig. 3**).



GLYCOSIDIC SWITCH CANDIDATES



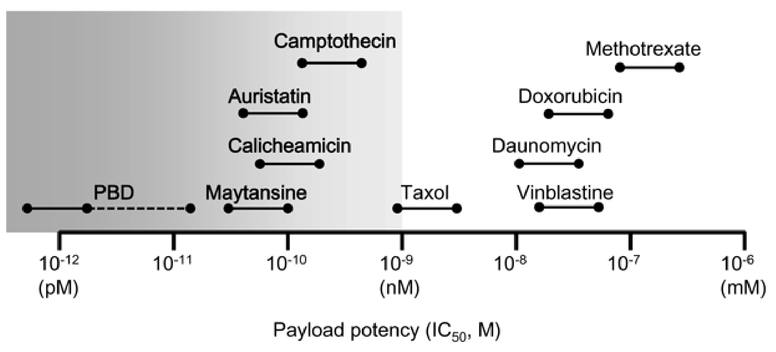


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Fig. 1 Schematic diagram of glycosidic switch strategy for drug loading in liposomes and intracellular drug regeneration: A water-soluble glycosidic switch (G^W) is attached to a hydrophobic drug to generate a water-soluble drug (Drug-G^W). The glycosidic switch can be esterified to produce a lipid-soluble form (Drug-G^L) to facilitate active loading in liposomes. At a high internal pH in the aqueous lumen of the liposomes, the glycosidic switch is spontaneously saponified to the water-soluble form, resulting in strong retention of Drug-G^W. Drug-G^W liposomes are stable in circulation and can be safely delivered to tumors for cellular uptake. The glycosidic switch on Drug-G^W is enzymatically removed by the lysosomal enzyme beta-glucuronidase to regenerate the parental drug inside cancer cells. Some GS drug targets are shown on the right.

RESULTs

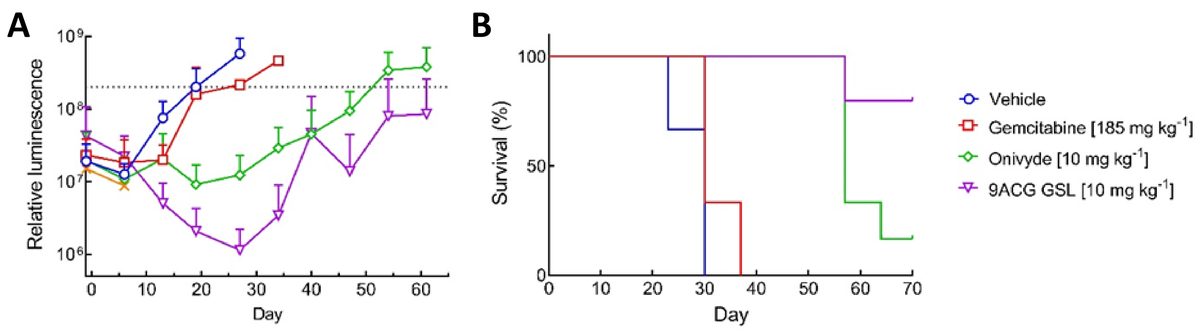

Fig. 2 9ACG GSL displays antitumor activity against human pancreatic cancer. Groups of three NOD-SCID mice were orthotopically injected with CFPAC-1/Luc human pancreatic cancer cells. After 12 days, mice received the vehicle, 185 mg/kg gemcitabine, 10 mg/kg Onivyde® , or 10 mg/kg 9ACG GSL via i.v. injections every week for 5 weeks. (A) Bioluminescence image, and (B) mean *in vivo* luminescence signals from cancer cells measured on an IVIS imaging system. (C) Mice survival rate.

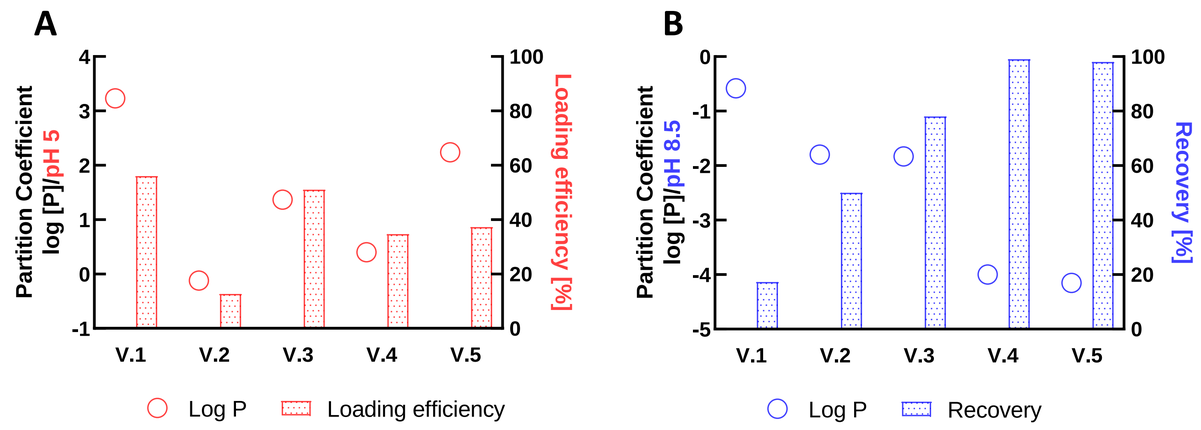

Fig. 3 Effects of modulated MMAE-G derivatives. **A.** The log*P* of the lipid-soluble form at pH 5, higher values demonstrate its hydrophobicity which facilitates the loading efficiency of GSL. B. The log*P* of the water-soluble at pH8.5, lower values demonstrate its hydrophilicity, which stabilized the drug’s retention inside the liposome.

Table 1. Partition Coefficient and Relevant GSL Parameters of SN-38G Derivatives

SN-38G	pH 5, loading efficiency of drug^L		pH 8.5, stability of drug^W retained	
	Log P of drug^L	Loading efficiency (%)	Log P of drug^W	Recovery after dialysis(%)
R1*	0.36	80	-3.7	100**
R2	0.85	67	-3.4	100**
R3	1.3	59	-3.2	100**

*R1, shows the best loading.
**Loaded SN-38G is stable inside the liposome.

Table 2. Partition Coefficient and Relevant GSL Parameters of MMAE-G Derivatives

MMAE-G	pH 5, loading efficiency of drug^L		pH 8.5, stability of drug^W retained	
	Log P of drug^L	Loading efficiency (%)	Log P of drug^W	Recovery after dialysis(%)
V.1	3.2	56	-0.58	17
V.2	-0.12	13	-1.8	50
V.3	1.4	51	-1.8(OMe$^{1/2}$)	78
V.4	0.4	35	Est. -4	100
V.5*	2.4	37	-4.2	98

* V.5 possesses rational hydrophobicity for GSL loading and extreme hydrophilicity for stabilizing the drug’s retention inside the liposome.