**Title:** “Sphingomyelin-derived Camptothecin Nanovesicles for Safe and Synergistic Cancer Immunochemotherapy”

**Abstract:** Despite the enormous therapeutic potential of immune checkpoint blockade (ICB), it benefits only a small subset of patients. Some chemotherapeutics can switch 'immune-cold' tumours to 'immune-hot' to synergize with ICB. However, safe and universal therapeutic platforms implementing such immune effects remain scarce. We demonstrate that sphingomyelin-derived camptothecin nanovesicles (camptothesomes) elicit potent granzyme-B- and perforin-mediated cytotoxic T lymphocyte (CTL) responses, potentiating PD-L1/PD-1 co-blockade to eradicate subcutaneous MC38 adenocarcinoma with developed memory immunity. In addition, camptothesomes improve the pharmacokinetics and lactone stability of camptothecin, avoid systemic toxicities, penetrate deeply into the tumour and outperform the antitumour efficacy of Onivyde. Camptothesome co-load the indoleamine 2,3-dioxygenase inhibitor indoximod into its interior using the lipid-bilayer-crossing capability of the immunogenic cell death inducer doxorubicin, eliminating clinically relevant advanced orthotopic CT26-Luc tumours and late-stage B16-F10-Luc2 melanoma, and achieving complete metastasis remission when combined with ICB and folate targeting. The sphingomyelin-derived nanotherapeutic platform and doxorubicin-enabled transmembrane transporting technology are generalizable to various therapeutics, paving the way for transformation of the cancer immunochemotherapy paradigm.