Nanoparticles enhance gemcitabine efficacy by overcoming fibroblast barriers in pancreatic cancer

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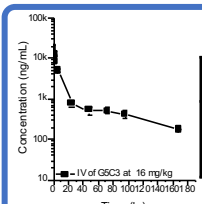
Abstract

Pancreatic cancer remains one of the deadliest malignancies, with poor surgical outcomes and treatment resistance contributing to low patient survival rates. A key barrier to effective therapy is the dense and heterogeneous extracellular matrix (ECM) within the tumor microenvironment (TME), which impedes drug penetration. Additionally, cellular interactions in the TME, particularly the activation of cancer-associated fibroblasts (CAFs) and the polarization of macrophages toward the immunosuppressive M2 phenotype, drive tumor progression and metastasis. In this study, we developed glucosamine-cholesterol (G-C) labelled liposomes encapsulating C8 ceramide (G5C3) to target both CAFs and pancreatic cancer cells under normoxic and hypoxic conditions. G5C3 exhibit selective cytotoxicity toward cancer cells and suppress CAF activity, thereby reducing the secretion of pro-tumorigenic factors and remodeling the TME. The *in vitro* experiments demonstrate that the liposomes undergo transcytosis from CAFs to cancer cells, highlighting their ability to penetrate the ECM and deliver therapeutic agents deep within tumor tissue, ultimately downregulating hypoxia-inducible and growth factor expression. Moreover, the treatment enhances reactive oxygen species (ROS) accumulation in macrophages while inhibiting M2 polarization, further disrupting the tumor-supportive microenvironment. ROS generation in cancer cells also promotes apoptosis. Collectively, these findings support the potential of this liposomal delivery system to overcome ECM-mediated drug resistance and improve therapeutic efficacy. When combined with gemcitabine, the current first-line chemotherapeutic, a strong synergistic effect was observed, underscoring the promise of this strategy for advanced pancreatic cancer treatment.

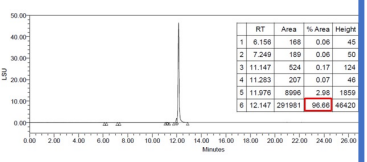
Keywords: Hypoxia-targeting, transcytosis, ceramide

Pharmacokinetic Study



Analyte	C^0 (ng/mL)	$t^{1/2}$ (hr)	MRT (hr)	$AUC^{(0\text{-last})}$ (ng*hr/mL)	$AUC^{(0\text{-}\infty)}$ (ng*hr/mL)	CL (mL/min/kg)	V_{ss} (L/kg)
G5C3	23435 ± 6127	64.8 ± 12.7	54.3 ± 4.96	160770 ± 11201	177385 ± 8260	1.51 ± 0.07	4.92 ± 0.70

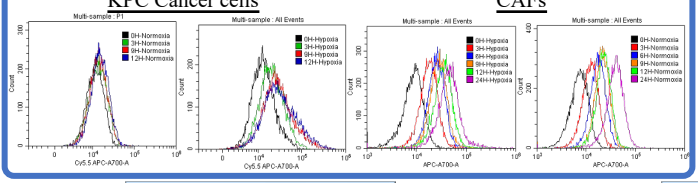
35-gram batch of G-C synthesis



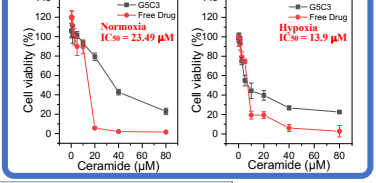
	RT	Area	% Area	Height
1	6.156	168	0.06	45
2	7.249	189	0.06	50
3	11.147	524	0.17	124
4	11.283	207	0.07	46
5	11.976	8996	2.98	1859
6	12.147	291981	96.66	46420

Purity : 96.66%

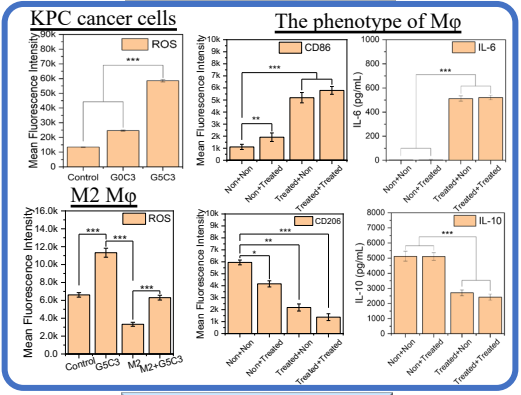
Targeted ability



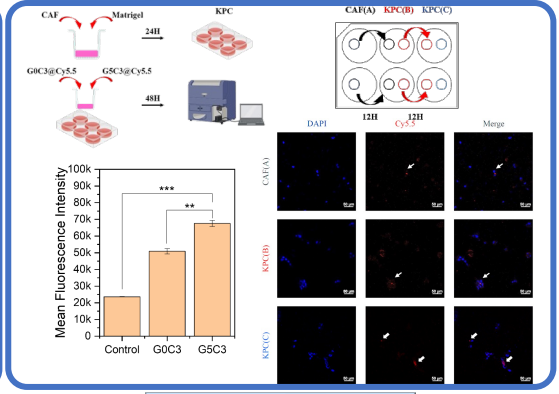
Cytotoxicity



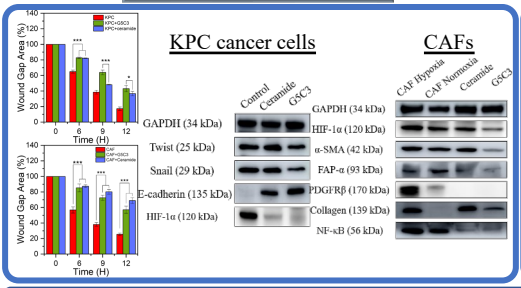
Macrophage Re-education



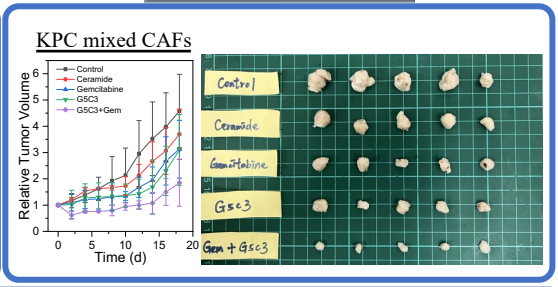
Transcytosis ability



The bio-activity of G5C3



In vivo of tumor inhibition



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Acknowledgements

The authors would like to thank the National Science and Technology Council, Taiwan (NSTC 113-2124-M-A49-006 and 111-2314-B-A49-050-MY3)