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Nanocarrier with reversibly hydrophobized co-drugs for treating aggressive neuroblastoma

David Guerrero, Ivan S. Alferiev, Ferro Nguyen, Peng Guan, Venkatadri Kolla, Danielle Soberman, Ilia Fishbein, Robert J. Levy, Garrett M. Brodeur, and Michael Chorny
Children's Hospital of Philadelphia, USA

Nanomedicine-based delivery strategies have the potential to improve the therapeutic performance of a variety of anticancer agents. However, their clinical translation has been hampered by difficulty in achieving stable drug entrapment within nanocarriers, together with controlled release directly in the tumor tissue. In this study, we evaluated an experimental strategy that combines in situ activatable camptothecin-mitocan fusion molecules (co-drugs) and sub-100nm sized biodegradable nanoparticles (NP) derived using a nanoprecipitation-based formulation process. A series of reversibly hydrophobized co-drugs of a potent camptothecin agent, SN38, with tocol mitocans exhibiting a range of hydrolytic activation rates were encapsulated in 85±36nm sized NP with high efficiency (93±2% entrapment yield) using the optimized procedure. NP loaded with a phenolic ester co-drug were found to be most effective against both chemo-naïve and chemoresistant NB cells under conditions modeling different levels of exposure experienced by NB cells within the tumor. Phenolic carbonate and aliphatic ester designs were found to be notably less efficient. In an *in-vivo* model of previously untreated disease [IMR-32 orthotopic xenograft], nanocarriers with phenolic ester co-drug administered over 4 weeks [10mg/kg, twice a week] induced tumor regression and completely inhibited tumor growth over a 26-week period. The same co-drug/nanocarrier formulation tested against multidrug-resistant NB [BE(2)-C orthotopic xenograft] potently suppressed tumor growth and extended animal survival up to 7 weeks, in contrast to a marginal and transient effect of the clinically used SN-38 precursor, irinotecan [event-free survival of 3 weeks vs. 2 weeks in 'no treatment' and drug-free NP groups]. We conclude that camptothecin-mitocan co-drugs can be rationally designed as therapeutic cargoes for nanocarrier-based therapy of aggressive malignancies. The co-drug/nanocarrier combination strategy proven effective in preclinical testing experiments in this study holds promise as a treatment for high-risk NB and potentially can be extended to other pediatric and adult solid tumors.

Biography

David Guerrero in 2015, joined the research team of Dr. Michael Chorny at The Children's Hospital of Philadelphia working on new drug delivery systems for treating arterial restenosis and cancer. Among other projects, he has worked on developing new strategies to target and treat aggressive pediatric solid tumors using polymeric nanoparticles formulated with novel mutual prodrugs (co-drugs). His research has contributed to a recent paper in Clin Cancer Res on enhanced intratumoral delivery of camptothecin-mitocan co-drugs for the treatment of high-risk neuroblastoma.

guerrerodt@email.chop.edu