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SN-38 prodrug-loaded nanoparticles for neuroblastoma therapy

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Camptothecin and its analogs are a family of potent small-molecule topoisomerase I inhibitors with a broad spectrum of activity against adult and pediatric cancers, whose safety, metabolic stability and therapeutic efficacy could potentially be greatly improved by using properly formulated nanocarriers. We developed a formulation strategy integrating prodrug modification and a NP preparation method producing sub-100 nm sized, bioeliminable NP for nanoencapsulation and delivery of a 7-ethyl-10-hydroxy analog of camptothecin, SN-38. A derivatization approach based on phenolic ester chemistry uniquely suited for creating rapidly activatable prodrug constructs was chosen to make a reversible, strongly lipophilic conjugate of SN-38 with tocopherol succinate (SN38-TS) for optimally stable incorporation into PEGylated NP, with a size adjusted to achieve high ingress efficiency and protracted retention in the target tissue. The specific contribution of this prodrug design to the potency and temporal pattern of the NP-mediated antiproliferative effect was examined in experiments comparing neuroblastoma cell growth inhibition by nanoencapsulated SN38-TS and its aliphatic ester isomer (isoSN38-TS). *In vivo* therapeutic efficacy of SN38-TS impregnated NP was next evaluated against established large tumors in a mouse xenograft model of neuroblastoma. The strong anticancer effect of the prodrug-loaded NP observed in our studies is highly relevant in the therapeutic context of neuroblastoma treatment. Our findings point to the importance of identifying and addressing critical formulation challenges for increasing effectiveness and improving translational potential of experimental nanomedicine-based approaches as new cancer treatment modalities.

Biography

Michael Chorny earned his PhD in pharmaceutical sciences at the Hebrew University of Jerusalem. Since 2009 he is an Assistant Professor of Pediatrics at the University of Pennsylvania and the Children's Hospital of Philadelphia. His research focuses on development and evaluation of biodegradable nanocarriers for targeted delivery of drugs, gene vectors and cells for cardiovascular disease applications and cancer therapy.

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