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PMLA nanoconjugates for effective delivery of antisense oligos: Optimization, mechanism, and brain tumor treatment

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Polymalic acid (PMLA) is a naturally occurring biodegradable polymer suitable for drug delivery. In order for PMLA copolymers to deliver antisense oligos into cyteoplasm, they must acquire the capability to cross the cytoplasm membrane. We designed and synthesized dozens of PMLA copolymers, and found PMLA copolymers of leucine ethyl ester (P/LOEt) or trileucine (P/LLL) show either pH-independent or pH-dependent activity for membrane penetration. The two copolymers displayed distinctly different properties in solution and during membrane permeation: P/LOEt binds extensively to membrane causing permeation through a "carpet" model; in contrast, P/LLL self-assembles to form oligomers pH-dependently (pKa 5.5) and induces membrane pores through a "barrel-stave" model. Both copolymers were selected for the delivery antisense oligos for the treatment of glioma. Malignant gliomas are the most aggressive and lethal brain tumors. Currently, effective glioma treatment drugs are still very limited. Nanoconjugates based on membrane permeant PMLA copolymers P/LLL and P/LOEt were synthesized for glioma treatment. The nanoconjugates were designed to bypass two major barriers, brain tumor barrier (BTB) and tumor cell membrane, containing three key functional components: monoclonal antibodies to transferrin receptor; cleavable antisense oligonucleotides (AONs) for inhibition of laminin-411 synthesis; and membrane permeable endosome escape unit. They demonstrated efficient cytoplasmic delivery of AON for significant inhibition of laminin-411 synthesis *in vitro* and *in vivo*, specific accumulation in brain tumor cells, inhibition of tumor angiogenesis and effective suppression of intracranial glioma growth.

Biography

Hui Ding has extensive research experience in drug delivery, biomaterials, and cancer treatment. He received his BS from Beijing Medical University and completed his PhD in the Department of Pharmaceutics and Pharmaceutical Chemistry at the University of Utah in 2006. He started his post doctoral research in the Department of Neurosurgery at Cedars-Sinai Medical Center working on the brain and breast tumor treatment using polymalic acid as drug delivery system. He continued his research on drug delivery and naomedicine as research scientist after 2010 and assistant professor after 2012 at Cedars-Sinai.

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