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Novel FOXM1/proteasome inhibitor Thiostrepton encapsulated in nanoparticles inhibits tumor growth

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The oncogenic transcription factor FoxM1 is an attractive therapeutic target in the fight against cancer, because it is overexpressed in a majority of human tumors, while its expression is usually halted in normal non-proliferating cells. We identified thiazole antibiotics Siomycin A and thiostrepton as inhibitors of FoxM1 transcriptional activity. In addition, we demonstrated that thiostrepton and Siomycin A downregulate FoxM1 protein and mRNA levels and act as proteasome inhibitors. We encapsulated thiostrepton into micelles assembled from amphiphilic lipid-PEG (polyethylene glycol) molecules, where thiostrepton is solubilized within the inner lipid compartment of the micelle. Upon assembly, hydrophobic thiostrepton molecules are solubilized into the lipid component of the micelle shell, formed through the self-assembly of amphiphilic lipid-PEG molecules. Maximum accumulation of micelle-thiostrepton nanoparticles (100 nm in diameter, -16 mV in zeta-potential) into tumors was found at 4 hours post-administration and was retained for at least 24 hours. Upon continuous treatment, we found that nanoparticle-encapsulated thiostrepton reduced tumor growth rates of MDA-MB-231 and HepG2 cancer xenografts. Furthermore, we show for the first time the *in vivo* suppression of the oncogenic FOXM1 after treatment with thiostrepton. Our data suggest that the thiazole antibiotic/proteasome inhibitor thiostrepton, when formulated into nanoparticles, may be highly suited as a nanomedicine for treating human cancer. Furthermore, we found that combination of thiostrepton in nanoparticles and bortezomib reduced tumor growth rates more efficiently than compared with when administered alone in xenograft and DEN-PB models of human cancer.

Biography

Andrei L. Gartel has completed his Ph.D. in Molecular Biology in age 28 from Moscow Institute of Virology, Russia. He is an Associate Professor of Molecular Genetics in the Department of Medicine at UIC. He published more than 80 papers in peer review journals and 25 papers in last three years. In addition he is academic editor of PLoS ONE and member of editorial boards of the following journals: *Antibiotics*, *Recent Patents on DNA and Gene Sequences*, *Open Biotechnology Journal* and *The Open Virology Journal*.

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