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Micelle-encapsulated novel proteasome inhibitor Thiostrepton is an effective nanomedicine against cancer

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We identified the thiazole antibiotic thiostrepton as an inhibitor of oncogenic transcription factor FOXM1 and as a proteasome inhibitor found to induce apoptosis in cancer cells. We encapsulated thiostrepton into micelles assembled from amphiphilic lipid-PEG (polyethylene glycol) molecules and solubilized into the lipid component of the micelle shell. Maximum accumulation of micelle-thiostrepton 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 human cancer xenografts. Furthermore, we showed the suppression of the oncogenic FOXM1 *in vivo* and increased apoptosis in the treated tumors, as indicated by cleaved caspase-3 expression. 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. Previously, we had shown the synergic effect of proteasome inhibitors bortezomib and thiostrepton in human cancer cell lines, where sub-apoptotic concentrations of both proteasome inhibitors resulted in synergic increase in cell death when combined as a treatment. Here, we administered such a combination to xenograft tumors *in vivo*, and found that the combination treatment with two proteasome inhibitors reduced tumor growth rates more efficiently than compared to when administered alone. Further examination additionally revealed that combination-treated tumors exhibited reduced proteasome activity, compared to non-treated and single drug-treated tumors. In addition, we showed the efficacy of thiostrepton-micelles inhibiting tumor growth in DEN/PB hepatocellular carcinoma mouse model. We also demonstrated enhanced anti-cancer effect of the combination treatment of thiostrepton with bortezomib. Our data suggest that micelle-encapsulated thiostrepton can be used against cancer.

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