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Thiostrepton as an Inhibitor of Cancer Stem Cell Growth and a Potential Enhancer for Chemotherapy in Non-small Cell Lung Cancer

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The presence of cancer stem-like cells (CSCs) has contributed to treatment resistance and disease recurrence. Thus, identifying agents that can selectively eliminate CSCs may lead to a more effective therapeutic strategy. Here, we used CSC-associated gene signatures to query Connectivity Map for identifying potential drug candidates that display the property to reverse the CSC gene signature. Thiostrepton, a natural cyclic oligopeptide antibiotic, was identified as the top candidate in this bioinformatics search. Thiostrepton' inhibitory effects on CSC population have been further supported by the reduced expression of cancer stemness markers, including CD133, Nanog, and Oct4A, in non-small cell lung cancer (NSCLC) cell lines. In addition, metastasis-associated Src tyrosine kinase signaling, cell migration, and epithelial-to-mesenchymal transition (EMT) processes were all inhibited by thiostrepton treatment. Thiostrepton in combination with gemcitabine synergistically suppressed NSCLC cell growth. More importantly, thiostrepton suppressed NSCLC tumorigenesis in vivo. Mechanistically, thiostrepton treatment led to the increased level of tumor suppressor miR-98 and reduced stemness and EMT markers. Our study demonstrated that thiostrepton, an old drug identified *in silico*, is an inhibitor for CSC renewal and a potential enhancer for chemotherapy in NSCLC.