Polymeric micelles of a novel inhibitor of DNA repair enzyme, polynucleotide kinase/phosphatase (PNKP), for targeted treatment of non-small cell lung cancer as monotherapy or in combination with Irinotecan

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Our research team has previously identified that the concomitant disruption of polynucleotide kinase/phosphatase (PNKP), an enzyme involved in DNA repair, and the tumor suppressor protein phosphatase and tensin homologue (PTEN), lead to synthetic lethality in different cancer models. Downregulation of PTEN is a frequent observation in non-small lung cancers (NSCLC), thus, pharmacological disruption of PNKP is expected to provide a viable and targeted mono-therapeutic strategy in NSCLC. Inhibition of PNKP can also make NSCLC more susceptible to cytotoxic effects of topoisomerase I inhibitors. Recently, the development of a potent PNKP inhibitor, namely A83B4C63, and its polymeric micellar formulations has been reported by our group [1]. The aim of the present study was to develop polymeric micelles of A83B4C63 modified on their surface with peptides targeting NSCLC cells. We also assessed the activity of A83B4C63 in NSCLC cell lines expressing different levels of PTEN expression as monotherapy or in combination with irinotecan. Polymeric micellar formulations modified on their surface with H2009 peptide have shown specific interaction with NSCLC cells overexpressing αvβ6-integrin. The PTEN positive NSCLC cells, i.e., H1975 cells, did not show loss of viability upon treatment with A83B4C63 monotherapy as shown by MTS and colony-forming assays. The PTEN-deficient H1299 cells, on the other hand, showed less growth and colony formation following treatment with A83B4C63 monotherapy. Treatment with A83B4C63 made both cells, more sensitive to Irinotecan. The sensitization effect of A83B4C63 upon combination therapy with irinotecan was significantly enhanced for H1299 over H1975 cells. The results imply a potential for polymeric micellar formulations of A83B4C63 as mono-therapeutics in PTEN deficient NSCLC cells and/or as targeted sensitizers to topoisomerase I inhibitors in NSCLC models.