Cross-Linked Hyaluronic Acid-Lipoic Acid Micelles for Enhanced Solubility, Stability and Targeted Delivery of Curcumin to Breast Cancer Cells
Y. Gao, M. Sarfraz, S. D. Clas, W. Roa, R. Loebenberg
University of Alberta

Purpose
The aim of this study was to develop a new nano-sized system for the delivery of curcumin (CUM) to breast cancer cells.

Methods
New amphiphilic conjugates were synthesized by chemical conjugation of hydrophobic lipoic acid (LA) to the hydrophilic hyaluronic acid (HA). Their chemical structure was investigated by 1H-NMR, IR and elemental analysis. CUM loaded micelles were characterized by DSC and XRD. The inhibitory effect of CUM loaded micelles was evaluated on human breast cancer cells MDA-MB-231. The intracellular distribution was investigated by confocal laser scanning microscope (CLSM). In addition, the uptake mechanisms of CUM loaded micelles were determined using uptake inhibitors.

Results
The new conjugates can self assemble into micelles (HA-LA) in aqueous solution. The micelles can be cross-linked (Cro) by dithiothreitol to form Cro-HA-LA, with a particle size of 120-180 nm. Compared with that in HA-LA, CUM in Cro-HA-LA has a smaller particle size, higher colloidal stability, higher drug loading as well as a lower release rate. Cro-HA-LA also significantly enhanced the aqueous solubility and stability of CUM. Furthermore, CUM in Cro-HA-LA micelles have the higher potency in inhibition the growth of MDA-MB-231 cells for 96h than the free CUM, while blank micelles are biocompatible with no toxicity observed at the concentrations up to 400 μg/mL. CLSM studies showed that CUM in Cro-HA-LA localized in both cytoplasm and nucleus. Finally, CUM in Cro-HA-LA micelles were taken up by MDA-MB-231 cells via a combination of caveolae, clathrin and lipid raft as well as HA receptor mediated endocytosis, with dose and energy dependent pathway.

Conclusion
These results reveal the promising potential of Cro-HA-LA micelles as an effective nano-vehicle for targeted cancer treatment.