Lipid Bilayer-Supported Mesoporous Silica Nanoparticle Composite for Synergistic Co-Delivery of Axitinib and Celastrol in Multi-targeted Cancer Therapy
H. B. Ruttala¹, J. Y. Choi¹, T. Ramasamy¹, R. K. Thappa¹, H. T. Nguyen¹, D. S. Kim², H-G. Choi², C. S. Yong¹, J. O. Kim¹
¹Yeungnam University, ²Hanyang University

Purpose
Small-molecule drug combination therapies are an attractive approach to enhancing cancer chemotherapeutic responses. Therefore, this study aimed to investigate the potential of axitinib (AXT) and celasterol (CST) in targeting angiogenesis and mitochondrial-based apoptosis in cancer.

Methods
We prepared AXT/CST-loaded combination nanoparticles (ACML) with CST loaded in the mesoporous silica nanoparticles (MSN) and AXT in PEGylated lipidic bilayers. The inhibition of angiogenesis and mitochondrial apoptosis by ACML was demonstrated in neuroblastoma (SH-SY5Y), squamous carcinoma (SCC7), and breast cancer (BT474) cell lines. Furthermore, an SCC7-bearing xenograft tumor model was developed to evaluate the synergistic therapeutic efficacy of ACML.

Results
We showed that ACML effectively inhibited angiogenesis and mitochondrial function and was efficiently internalized in SCC-7, BT-474, and SH-SY5Y cells. Furthermore, hypoxia-inducible factor (HIF)-1α expression, which increased under hypoxic conditions in all cell lines exposed to ACML, markedly decreased, which may be critical for tumor inhibition. Western blotting showed the superior anticancer effect of combination nanoparticles in different cancer cells. Compared to the cocktail (AXT/CST), ACML induced synergistic cancer cell apoptosis. The AXT/CST-based combination nanoparticle synergism might be mediated by AXT, which controls vascular endothelial growth factor receptors while CST acts on target cell mitochondria. Importantly, ACML-treated mice showed remarkably higher tumor inhibition (64%) than other groups did in tumor xenograft models. Tumor xenograft immunohistochemistry revealed elevated caspase-3 and poly (ADP-ribose) polymerase and reduced CD31 and Ki-67 expression, clearly suggesting tumor apoptosis through mitochondrial and antiangiogenic effects.

Conclusion
Overall, our results indicate that ACML potentially inhibited cell proliferation and induced apoptosis by blocking mitochondrial function, leading to enhanced antitumor efficacy.