**Preventing The Tumor Metastasis By Reigniting The Cancer-Immunity Cycle With Nanomedicine**

**Bao Loc Nguyen1**, Arief Kurniawan1, Jong Oh Kim1, Jeonghwan Kim1.

1College of Pharmacy, Yeungnam University, Gyeongsan 38541, Republic of Korea

**Background and aims.** Tumor metastasis is usually associated with an advanced stage of the tumor progression when the tumor cells completely escaped the immune surveillance and migrated to the distant organs. Although the induction of immunogenic cell death (ICDs) to restore the cancer-immunity cycle (CIC) using nanomedicine received a large attention, many challenges such as the mononuclear phagocyte system and insufficient accumulation in tumor cells hinder an effective therapeutic. Herein, we designed and prepared a nanomedicine which could effectively restimulate the CIC and inhibit the metastasis in different phases of the tumor progression.

**Methods.** Nanomedicine (LTX/IC-NP@CD47p) co-delivering an oncolytic peptide (LTX-315) and a Toll-like receptor agonist (Poly(I:C)) was prepared accompanied by the decoration of CD47 mimicking peptide (CD47p). The restoration of cancer-immunity cycles after LTX/IC-NP@CD47p treatments was demonstrated in the 4T1 tumor-bearing mouse. Finally, the therapeutic effect of LTX/IC-NP@CD47p in different phases of tumor metastasis were demonstrated in the orthotopic and experimental metastasis models.

**Results.** LTX-315 and poly(I:C) were successfully loaded into the polymer-lipid hybrid structure of LTX/IC-NP@CD47p. The NPs were formed at a size of 120 nm with a neutral surface charge. LTX/IC-NP@CD47p showed a 7-fold lengthening half-life time in the circulatory system compared to free LTX-315. Decoration of CD47p on the NPs surface also increased the accumulation of NPs in the tumor tissues at 24 h post injection. Moreover, with the presence of CD47p on the surface, LTX/IC-NP@CD47p could avoid the surveillance of phagocytes such as dendritic cells and macrophages in the circulatory system and tumor tissues, leading to an enhanced accumulation of NPs in the tumor cells. LTX/IC-NP@CD47p effectively induced the ICD in the cancer cells followed by reigniting the cancer-immunity cycle in the treated mice. Thereafter, LTX/IC-NP@CD47p exhibited a capability to delay the development of metastatic tumor in both orthotopic and experimental metastasis models, extending the overall survival of the treated tumor-bearing mice, especially when combined with immune checkpoint blockade (ICB).

**Conclusion/Discussion.** LTX/IC-NP@CD47p was successfully prepared for reigniting the CIC in the tumor-bearing mice. LTX/IC-NP@CD47p treatments effectively reduced the metastatic tumors and enhanced the survival rate of treated mice, especially in the combination with ICB.

**References:**