**uPAR-Targeted Nanoparticles to Deliver Dasatinib to Therapy-induced Senescent Tumor Cells**

**Thi Oanh Oanh Nguyen1**, Jeonghwan Kim1, Jong Oh Kim1

College of Pharmacy1, Yeungnam University, 280 Daehak-Ro, Gyeongsan, 38541, Republic of Korea.

**Background and aims.** The urokinase-type plasminogen activator receptor (uPAR) has emerged as a promising marker for identifying cellular senescence. This study aimed to engineer a targeted nanocarrier system to deliver the senolytic drug dasatinib specifically to senescent cells exhibiting elevated uPAR expression following cancer therapy.

**Methods.** Senescence was induced in HCT-116 and MDA-MB-231 cancer cell lines using low doses of irinotecan and palbociclib, respectively, and characterized by senescence-associated features and uPAR upregulation. A design of experiments strategy was employed to optimize key parameters of uPAR-targeted nanoparticles tailored to deliver dasatinib to uPAR-overexpressing tumor cells. Cellular uptake and selective clearance of senescent cells were assessed in vitro, while in vivo studies evaluated the anti-tumor and anti-metastatic efficacy of the formulation.

**Results.** The optimized uPAR-targeted nanoparticles (L-DAS@AE-105) displayed a favorable particle size (117.9 ± 0.9 nm), zeta potential (−14.0 ± 1.6 mV), spherical morphology, and maintained stability for up to 72 hours in serum-enriched conditions. In vitro, senescent cells induced by irinotecan or palbociclib showed efficient uptake of L-DAS@AE-105, leading to enhanced cytotoxic effects. In vivo, the nanoparticles preferentially accumulated in tumors following pro-senescence treatment that elevated membrane-bound uPAR in cancer cells. The combination of irinotecan and uPAR-targeted nanoparticles significantly suppressed tumor progression in a colorectal cancer xenograft model. Furthermore, sequential administration of palbociclib and L-DAS@AE-105 yielded potent anti-metastatic activity in an orthotopic model of triple-negative breast cancer.

**Conclusion/Discussion.** uPAR-targeted nanoparticles enhanced dasatinib’s senolytic effects, improving tumor suppression when combined with irinotecan in colon cancer and palbociclib in triple-negative breast cancer models.

**References:**

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**Acknowledgements:** This work was supported by the National Research Foundation (NRF) of Korea Grant funded by the Korean Government (NRF 2022R1A5A2018865).