**Antiangiogenic Therapeutic mRNA Delivery Using Lung-Selective Polymeric Vector for Non-Small Cell Lung Cancer Treatment1**

**Ngoc Duy Le**, Jeonghwan Kim\*, Jong Oh Kim\*.

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

**Background and aims.** Therapeutic antibodies targeting vascular endothelial growth factor (VEGF) have demonstrated clinical efficacy in non-small cell lung cancers (NSCLCs) by inhibiting tumor angiogenesis. However, the therapeutic effects of systemically administrated anti-VEGF antibodies are often hindered in NSCLCs by their suboptimal accumulation in lung tissue and their adverse effects to healthy organs.2,3 In this study we overcome these challenges by engineered an antiangiogenic therapeutic mRNA delivery vector using lung-selective polymeric nanoparticles. We synthesized a mini library of poly(β-amino esters) and used them to fabricate nanoparticles encapsulating synthetic mRNA encoding bevacizumab, an anti-VEGF antibody used in the clinic.

**Methods.** The PBAEs were synthesized via Michael addition using bisphenol A glycerolate diacrylate, hydrophilic amines (1-(2-aminoethyl)pyrrolidine, 2-(2-aminoethyl)-1-methylpyrrolidine, or 4-amino-1-butanol), and dodecylamine. The polymers were then end-capped with monomer 1,3-diaminopropane, resulting in a small library of PBAEs. Bevacizumab mRNAs were synthesized via *in vitro* transcription reaction.

**Results.** The PBAEs were employed to formulate hybrid nanoparticles with helper lipid and PEGylated lipid for mRNA delivery. Screening and optimization were performed to enhance pulmonary protein expression. The protein coronas of lung- and spleen-targeting formulations were analyzed using proteomics, revealing distinctive features potentially contributing to their organ-selectivity. The optimized PBAE nanoparticles were accumulated in pulmonary endothelial cells (PECs) - the primary targets of VEGF for angiogenesis, leading to localized bevacizumab production in the lung and reduced systemic exposure. In an orthotopic NSCLCs model, in situ bevacizumab secretion enhanced VEGF blockage and suppressed tumor growth.

**Conclusion/Discussion.** This study provides evidence for the principle of delivering bevacizumab mRNA for the treatment of NSCLCs. PEC-selective bevacizumab mRNA delivery and the blockade of VEGF in pulmonary tissues were achieved via PBAE-based NPs, which could be advantageous for eradicating angiogenesis in NSCLCs. We acknowledge several limitations of this study, including a discrepancy between NP biodistribution and transfection sites after mRNA administration as well as partial validation of organ-selective mechanisms of the NPs. Despite these limitations, our findings highlighted the potential of combining synthetic mRNA with lung-targeted delivery vectors to enable localized production of therapeutic antibodies for lung cancer treatment.

**References:**

1 Le, N. D. *et al.* (2024) *ACS Nano* 18, 8392-8410

2 Bensch, F. *et al.* (2018) *Theranostics* 8, 4295-4304

3 Kamba, T. & McDonald, D. M. (2007) *Br J Cancer* 96, 1788-1795

**Acknowledgements**: This work was supported by the National Research Foundation (NRF) of Korea Grant funded by the Korean Government (NRF 2021R1A2C3009556, 2022R1A5A2018865).