Lung cancer is the second most common form of cancer with the highest mortality rate worldwide in 2020 despite the advances in targeted- and immuno-therapies. Metabolic reprogramming has been recognized as an essential emerging cancer hallmark in which altered metabolic pathways represent an attractive therapeutic target. Sodium Dichloroacetate (DCA), a pyruvate dehydrogenase kinase (PDK) inhibitor, effect has been investigated in various tumors. Building on the already published data, this pre-clinical study aims to explore the anticancer potential of DCA in lung cancer alone and in combination with chemotherapeutic and targeted therapies using two non-small cell lung cancer (NSCLC) cell lines namely, A549 and LNM35.

This project was addressed through the investigation of the impact of DCA on lung cancer cell viability, migration, invasion, and colony growth \textit{in-vitro} and on tumor growth and metastasis using the chick embryo chorioallantoic membrane (CAM) and the nude mice models \textit{in-vivo}. The anti-angiogenic potential of DCA, its safety profile, and the impact of its combination with the proposed chemotherapy and first-generation EGFR tyrosine kinase inhibitors (EGFR-TKI) were also investigated.

This study demonstrated that DCA causes a concentration- and time-dependent decrease in the viability of A549 and LNM35 cells and the growth of their colonies \textit{in-vitro}. Similarly, DCA slow-down the growth of A549 and LNM35 tumor xenografts in both the chick embryo CAM and nude mice models \textit{in-vivo}. DCA decreases the angiogenic capacity of human umbilical vein endothelial cells (HUVECs) \textit{in-vitro} by decreasing HUVECs tube formation and sprouting, suggesting the inhibition of tumor angiogenesis as a potential mechanism behind its anti-tumor growth effect. On the other hand, DCA did not inhibit the \textit{in-vitro} migration and invasion and the \textit{in-vivo} incidence and growth of lymph nodes metastases in nude mice xenografted with the highly metastatic lung cancer cells LNM35. Treatment with DCA did not show any significant side effects on the chick embryos viability or on the nude mice weight and survival. In addition, blood, kidney, and liver function tests showed no toxicity with DCA when compared to the control group. Finally, we demonstrated that DCA significantly enhanced the anticancer effect of cisplatin and erlotinib in LNM35 and gefitinib in both cell lines.

In summary, these findings demonstrate that DCA is a safe and promising therapeutic agent for lung cancer and pave the way for further pre-clinical studies validating the impact of DCA in combination with not only the first generation but also the second and third generation of EGFR-TKI \textit{in-vivo}.

**Keywords:** lung cancer, dichloroacetate, pyruvate dehydrogenase kinase, tumor growth, angiogenesis, chick embryo CAM.