Título del Proyecto	**Epigenomic Profiling of Liquid Biopsy and Immunotherapy Resistance in Lung Cancer (EPILUNAR)**
Nº de expediente asignado	AC24/00010
Abstract	Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of metastatic non- small cell lung cancer (mNSCLC). However, due to mechanisms of resistance, only a small proportion of patients benefit from this type of immunotherapy (IMT). Currently, there are no effective biomarkers in the clinic to predict the resistance to this treatment. Therefore, it is an urgent unmet clinical need to discover novel biomarkers in order to identify the patients who will benefit from the treatment while identifying the resistance mechanism that impairs its success. On the other hand, a major limitation in evaluating resistance in mNSCLC is the difficulty in obtaining a sufficient amount of lung tumor sample to test in the clinic. In this scenario, the study of circulating elements by liquid biopsy (LB), such as cell-free DNA (cfDNA), circulating tumor cells (CTCs) and long non-coding RNAs (lncRNAs), emerges as an excellent non-invasive source to personalize the clinical management of this treatment. Blood is the most frequently used source of fluid in LB, however, other fluids, such as malignant pleural effusions (MPEs), hold a promising use for mNSCLC due to their CTC content. Importantly, LB is useful for the detection of epigenetic alterations originated in tumors, such as changes in DNA methylation and lncRNAs. In this sense, methylation of cfDNA and CTCs, and the alteration of lncRNA levels, have recently been proposed as non- invasive resistance biomarkers for some types of treatments. However, the analysis of these epigenetic alterations in LB as biomarkers of resistance to ICIs is completely unexplored in mNSCLC. In this proposal we aim to discover novel non-invasive epigenetic biomarkers and mechanisms of resistance associated to ICIs in mNSCLC patients to personalize the clinical management of IMT. Nowadays, the discovery of epigenetic biomarkers is being facilitated by the development of artificial intelligence (AI) and epigenomics. Thus, we will take advantage of the fields of epigenomics, AI and LB to overcome IMT resistance in mNSCLC. Combining genome-wide cfDNA methylation and AI approaches, we will develop a non- invasive cfDNA methylation signature to predict the resistance to ICIs

	in mNSCLC. We will also perform the whole-genome profiling of DNA methylation in peripheral single-CTCs to discover novel biomarkers and mechanisms of IMT resistance. This project will also involve the creation of MPE-derived organoids, as new tumor models to validate resistance mechanisms. The role in IMT resistance of a new subtype of lncRNAs, called stable intronic sequence RNAs (sisRNAs), will be also evaluated. Altogether, this proposal will reveal non-invasive biomarkers to predict IMT resistance, also providing the discovery of new mechanisms that impairs the effect of this treatment and opening new avenues to study non-invasive alternatives to overcome the resistance to IMT in mNSCLC.
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Enlaces:	https://transcan.eu/output-results/funded-projects/epilunar.kl