**SCIENTIFIC CONTEXT**

The observation of an altered metabolic state in cancer cells dates back to the early 20th century when Otto Warburg observed that cancer cells preferentially utilise glycolysis over oxidative phosphorylation for growth, even in the presence of normal oxygen levels (Warburg 1956), a phenomenon known as the ‘Warburg effect’. Warburg argued that, ‘this altered metabolic state was the underlying cause for cancer’.

The molecular mechanisms driving an altered tumour metabolism have only recently begun to be understood as a result of large-scale genomic sequencing as well as advances in metabolomic profiling technologies. Recent studies have shown that many oncogenes, including Myc and Ras, impart an altered metabolic phenotype in cancer cells through the regulation of genes involved in central metabolic pathways such as glycolysis, fatty acid metabolism, oxidative phosphorylation, and the one carbon pool. Understanding Tumor Metabolism’ in Banff, Canada (since March), Eva P. Lospitao, Gloria Martínez Del Hoyo, Laura Díezma, Tamara Homdejar (TS), Sandra Penegreg (TS), Eslida Casas López (June December).

**SCOPE OF THE ELI LILLY - CNIO PARTNERSHIP**

Eli Lilly and CNIO are collaborating on the identification and validation of novel targets in cancer immunometabolism. Our Section is funded through a research contract with Eli Lilly and focuses on the identification of small molecular weight molecules that regulate the metabolism of malignant cells, with the objective of killing them, either directly, acting synergistically with other anti-tumour agents, or activating the anti-tumour immune response. Exploring how to better target these mechanisms would lead to better and more efficient therapeutic options. A combination of in vitro and in vivo approaches is being utilised to obtain a complete understanding of the metabolic reprogramming regulated by oncogenes like RAS, as well as the characterisation of the metabolic status of tumours (Cerezo A. et al, February 2016; Keystone symposium meeting on ‘New Frontiers in Understanding Tumor Metabolism’ in Banff, Canada). For this purpose, we have developed a series of biochemical and cell-based assays exploiting advanced techniques such as extracellular flux analysis (Seahorse technology), NMR and metabolomics. Finally, each target goes through an in vivo validation process using xenografts, allografts and mouse models developed at the CNIO; this process includes the use of non-invasive in vivo imaging technologies, as well as the immunohistochemical characterisation of tumours for different metabolic, immune and tumour markers.

**EXPERIMENTAL THERAPEUTICS PROGRAMME | CNIO - LILLY CELL SIGNALLING THERAPIES SECTION**

**Figure** (A) Immunohistochemical analysis of metabolic enzyme [PDH], showing the tumour microenvironment in a RAHM 6 from a Pancreatic Adenocarcinoma model (OVA (OVA); TetO-Cre; K-Ras(+/LSLG12V); P53(lox/lox); PDAC (Carmen Guerra & Mariano Barbacid)). In addition to the tumour cells, there are fibroblasts, endothelial, myeloid cells and immune cells that may be facilitating tumour growth, while the immune cells involved in the anti-tumour immune response are absent or inhibited. (B) Immunohistochemical analysis showing that the expression of the immune checkpoint ligand PD-1 correlates with the expression of specific tumour profiling markers (LDHH, FASN) and certain metabolic markers (LDHH and FASN). In a lung adenocarcinoma derived from a XentrZLD/Gpex (PDEx/Ex) Chima Ambrogio & Mariano Barbacid). (C) Cartoon depicting a strategy to control tumour growth through the regulation of specific metabolic targets. Tumours may rely heavily on specific metabolic pathways to grow and evade immune surveillance, as well as to obtain energy. This rapid growth also results in increased DNA damage, either through an increase in the production of ROS or due to replication stress. This situation leaves tumour cells more vulnerable to certain metabolic interventions as well as increasing the anti-tumour response of the immune system.