



Juan Velasco

Section Head (acting)

Juan Velasco was born in Ciudad Real in 1965. He obtained his degree in Biology at the *Universidad Complutense de Madrid* where he also earned his PhD with honours in 1994.

He initiated his research career at Georgetown University Medical Center, Washington DC (USA), where he isolated and identified the novel oncogene activated by chemical carcinogens PcpH, under the leadership of V. Notario in the Experimental Carcinogenesis Division.

In 1996 Juan Velasco returned to Spain to join the *Instituto de Investigaciones Biomédicas "Alberto Sols"* (Madrid) as a Research Associate in the laboratory of P. Santisteban. During this time, his research focused on the molecular mechanisms of radiation-induced carcinogenesis.

From 1998 to 2001 Juan joined Mariano Barbacid's laboratory at the CNIO as a Research Scientist. His research addressed the preclinical validation of farnesyl transferase as a molecular target using genetically engineered mice.

Juan Velasco later joined Eli Lilly and Company at the Discovery Research site in Alcobendas (Madrid), where he created the Biochemistry and Cell Biology Laboratory focused on the development of biological assays used to define the therapeutic and antitumour activities of new molecular entities. Currently, Juan Velasco holds the position of Director of Translational Sciences and Technologies at Lilly Research Laboratories.

Summary

This section is funded through a research agreement with Eli Lilly & Company, a global pharmaceutical leader in the discovery, development and commercialisation of innovative drugs. The scope of our research focuses on the identification and validation of novel targets in cancer metabolism.

Main Objectives

- Evaluate new cancer targets in the context of cell signalling and metabolism
- Apply cell and molecular biology techniques including gene knock-down and overexpression for phenotypic characterisation
- Explore *in vivo* tumour biology to determine the importance of key targets in cancer metabolism





Staff scientists: Bastien Cautain (until July) and Carmen M. Pérez. **Technicians:** Nuria Bravo (since June), Laura Diezma, Eva P. Lospitao and M. Cristina Osuna (since June).

Highlights

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, who was awarded the Nobel Prize in 1931, argued that this altered metabolic state was the underlying cause for cancer. Although Warburg's hypothesis was overshadowed for a number of years by increased interest in the genetic basis of cancer, the "Warburg effect" is still widely accepted in the field. The preferential use of glucose by tumour cells has been exploited clinically to image cancer through the utilisation of ¹⁸F-fluorodeoxyglucose-positron emission tomography (¹⁸F-FDG-PET). Changes in the FDG-PET signals are often used as an early predictor of response to chemotherapy. The molecular mechanisms driving

the glycolytic phenotype have only recently begun to be understood as a result of large scale genomic sequencing as well as advances in metabolomic profiling technologies. In addition to enhanced glycolysis, the work of C. Dang and others has established a critical role for glutaminolysis in Myc oncogene-dependent tumour cells. Recent publications demonstrated that targeting key enzymes in the glutamine metabolic pathway can limit tumour growth in preclinical xenograft cancer models. This mechanistic understanding of cancer metabolism has led to renewed interest in developing therapeutics to target key enzymes that drive tumour metabolism.

A number of oncogenes and tumour suppressors have now been identified as key effectors in modulating cell metabolism (Figure). Genome sequencing studies have uncovered somatic mutations in metabolic enzymes including succinate dehydrogenase (SDH), fumarate hydratase (FH) and isocitrate dehydrogenase (IDH). The loss of function mutations in SDH and FH impart a glycolytic phenotype in tumour cells, possibly through inhibition of the HIF-directed prolyl hydroxylases that are required for HIF degradation in the presence of oxygen. In addition to mutations in metabolic enzymes, recent studies have shown that many oncogenes, including Myc and Ras, impart a glycolytic phenotype in cancer cells by upregulating the expression of genes involved in glycolysis (e.g. *GLUT-1*, *PDHK*, *LDH5*). Von Hippau Lindal (VHL), an E3 ligase required for HIF-1 degradation, is a tumour suppressor that is deleted in almost 50% of kidney cancers. The loss of VHL results in the stabilisation of HIF1, even in the presence of oxygen, and imparts a glycolytic phenotype with enhanced glucose uptake and high levels of lactate production.

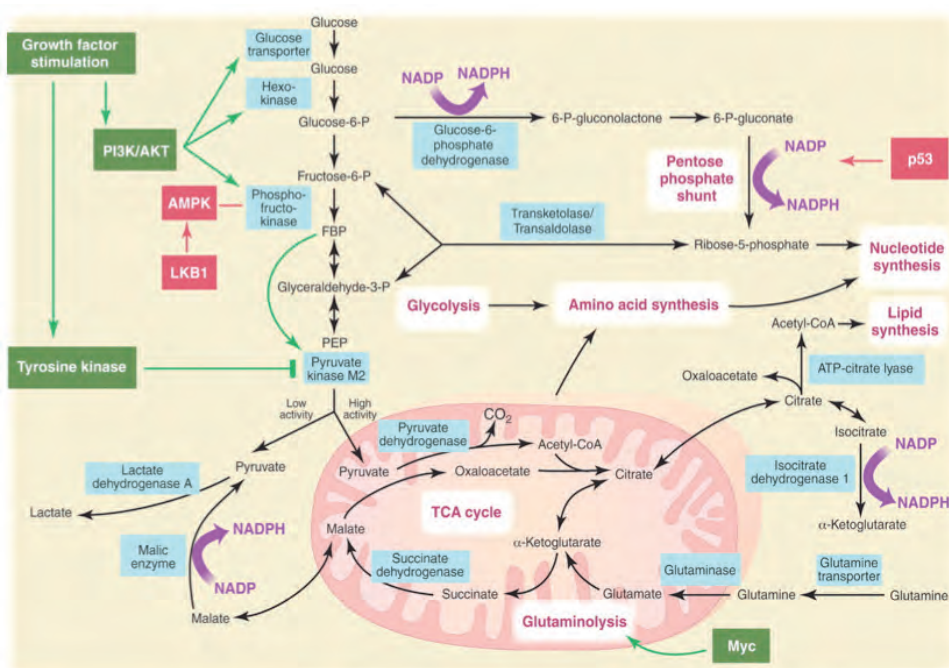


Figure: Key metabolic pathways driving tumour cell growth and proliferation (taken from Vander Heiden M.G., Cantley L.C. et al. (2009). *Science* 324, 1029).