

Molecular Pharmacology Section



Ana Rodríguez

Section Head

Ana Rodríguez was awarded her PhD in Biology at the *Universidad de Salamanca* in 1996 for her work on the proliferation and apoptosis processes involved in the development of glomerulosclerosis. During this time she was also a Fellow at the Department of Medicine, Rayne Institute, University College of London Medical School (UK).

The following five years of her career were spent in the UK. Firstly she was a Postdoctoral Research Associate at the CRC Pharmacology Group, the School of Biological Sciences, the University of Manchester. She then moved to the Department of Biochemistry at the University of Oxford. Her research during this period focused on different aspects of cancer and ageing.

She returned to Spain to work as Head of the Genomics Unit for the company *Genómica SAU* in Madrid. She joined the CNIO in 2004 to lead the Cell Signalling Therapies Group where she was responsible for a collaborative project with the pharmaceutical company Eli Lilly. In January 2010 she was appointed Head of the Molecular Pharmacology Section, the Experimental Therapeutics Programme.

Summary

The PI3K/Akt and the JAK/STAT signalling pathways are frequently activated by mutations in human cancer and are therefore considered potential intervention points for anti-cancer therapeutics. For this reason we have been pursuing the identification and characterisation of selective inhibitors of PI3K α as well as selective inhibitors of the PIM Kinases which are key downstream effectors of JAK/STAT signalling in tumour cells.

An additional target under evaluation is CDK8, a component of the Mediator complex, which couples the action of transcription factors with the molecular transcriptional machinery. CDK8 is located at chromosome region AT 13q12,13, a region of recurrent copy number gain in colon cancer.

Main Objectives

- Elucidation of the biological mechanism of action of novel anti-cancer therapeutics in tumour cells
- Validation and characterisation of new compounds that target the PI3K/Akt and Jak/STAT signalling cascades
- CDK8 target validation and cellular assay development
- Development of mouse models that recapitulate the genetics and physiology of human tumours





Staff scientists: Carmen Blanco, Wolfgang Link and Oliver Renner. **Graduate student:** Maja Narlik. **Technicians:** Nuria Ajenjo, Beatriz García, Belén Pequeño, Sandra Peregrina, M. Teresa Merino (until August), Jara Moreno (until January) and Natasha Zarich.

Highlights

Inhibitors of the PI3K signalling pathway are of great therapeutic interest in oncology. We have identified an imidazopyrazine derivative, ETP-46321, that elicits a mechanism of action both *in vitro* and *in vivo* consistent with PI3K inhibition. The biological characterisation of this compound showed that treatment of cells with ETP-46321 leads to a reduction in the level of Akt phosphorylation as well as phosphorylation of GSK3 β and p70S6K (Figure, panel A).

This compound exhibits antiproliferative activity in a variety of tumour-derived cell lines, which appears to be independent of the PI3K α and PTEN mutational status. We should mention however that this process involved the profiling of a small number of cell lines and that more extensive tumour cell profiling could reveal some sensitivity or resistance based upon the p110 α or PTEN status (Figure, panel B).

The aberrant activation of the canonical WNT/ β -catenin pathway occurs in almost all colorectal cancers and contributes to their growth, invasion and survival. CDK8 is a positive regulator of genes within the β -catenin pathway.

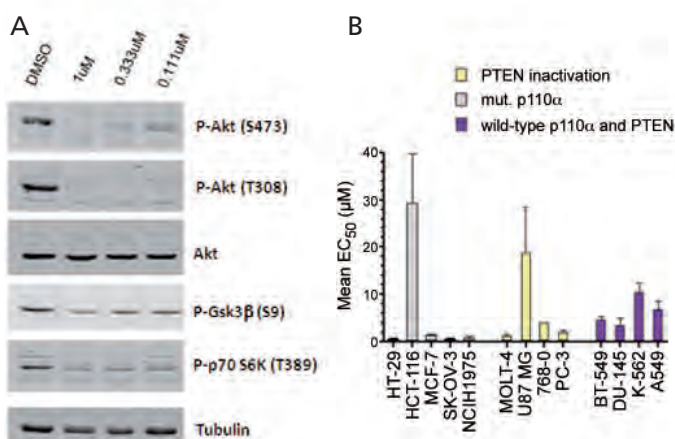


Figure: (A) Dose dependent inhibition of the PI3K pathway in U2OS cells treated with ETP-46321(1h); (B) Anti-proliferative activity of 10 μ M ETP-46321 alone in different cell lines.

We are in the process of validating CDK8 as a target for colon cancer. Furthermore, we have developed and validated two cellular assays for the screening of potential compounds – one is based on β -catenin-CDK8 mediated transcription and the other on the CDK8-dependent control of the serum response network, including several members of the early growth response family of oncogenic transcription factors.

Publications

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