



## Experimental Therapeutics Medicinal Chemistry Department



### Joaquín Pastor Fernández

Department Director

The main goal of the Department of Medicinal Chemistry is to discover novel anti-cancer compounds, optimise their biological activity, selectivity, safety, and preclinical properties, thereby creating a product of high value for clinical development.

For the PI3K project, we have identified a number of selected PI3K inhibitors with good biochemical/cellular activity and a clean selectivity profile versus other kinases. These compounds have demonstrated a good PK/PD correlation after oral administration and *in vivo* efficacy in several tumour xenograft and transgenic models that is comparable, or even better, to other reference compounds under clinical investigation.

Regarding the PIM inhibitor project, we are in an advanced "hit to lead" phase for several chemical series. We have obtained highly potent and selective compounds against a panel of 24 representative kinases and identified ADME-related issues that need to be optimised in the next phase of the process. Our priority is to select several compounds and promote them for *in vivo* studies, to reach proof-of-concept for this target. In collaboration with Guillermo Montoya, from the CNIO Macromolecular Crystallography Group, we generated crystallographic and structural

information on several ETP and reference compounds regarding the ATP binding pocket of PIM1.

CDK8 is another target at the hit identification/generation phase. We carried out an HTS campaign and obtained several hits, providing Intellectual Property (IP) with poor diversity within the chemical space (non-free position IP), as well as free space IP (a free IP situation). These results are currently under analysis by medicinal chemists.

The ATR inhibition project is the result of a collaborative project with Óscar Fernández-Capetillo from the CNIO Genomic Instability Group. Óscar developed the cellular assay for the project and has carried out a screening campaign using several selected compounds from our library. A focused Medicinal Chemistry Programme was initiated detecting a number of hits in the low nanomolar range.

We have also established collaborations with other CNIO Groups, including Manuel Serrano's Tumour Suppression Group for the selection of proprietary PI3K inhibitors and their potential application as anti-ageing and anti-obesity compounds. This work has led to filing a joint application for a patent.

### Biosketch of Joaquín Pastor Fernández

Joaquín Pastor was born in Madrid in 1964. He graduated from the *Universidad de Alcalá* in 1987 and obtained his PhD in 1994.

He joined K.C. Nicolaou's Group at The Scripps Research Institute, La Jolla, USA, as a Postdoctoral Fellow until 1998, where he worked on several projects aimed at the total synthesis of natural products with biological interest, such as the Epothilones, molecules approved by the FDA as anticancer agents.

Pastor was appointed as Head of High Throughput Medicinal Chemistry (HTMC) at Janssen Pharmaceutical, Spain, in 1998. The HTMC group was key in the implementation of Parallel Synthesis Technology and actively participated in projects (Oncology and CNS), which produced 2 clinical candidates.

In 2004 he was appointed as Head of HTMC and Analytical and Purification Technology Groups at

Janssen, Belgium, where he was responsible for the design and preparation of chemical libraries, in particular, Protein Kinase inhibitors. He then returned to Spain as Leader of CNS and European Lead Generation Groups.

He joined the CNIO as Director of Medicinal Chemistry, the Experimental Therapeutics Programme in June 2008, where he has played a key role in the implementation of diverse hit/lead generation strategies to complement HTS techniques, with an emphasis on clinical compounds as a source for new drug designs. He also supports the early assessment of selected compounds in *in vivo* settings to derive *in vitro-in vivo* correlations as predictive tools in drug discovery.

He has authored more than 45 peer-reviewed articles and patents.