

Animal Pharmacology Section



Teresa González-Granda

Section Head

Born in Asturias, Teresa González-Granda obtained her PhD in Biology in 1996 at the *Universidad de Oviedo*. Supported by a Marie Curie Fellowship, she joined the laboratory *Chronothérapeutique du cancer* in Villejuif (France) at the *Institut National de la Santé et de la Recherche Médicale* (INSERM). She continued her postdoctoral training in the same institution with a grant from the *Ligue Nationale Française Contre le Cancer* until she was promoted to Research Scientist. She was involved in several projects on the optimisation of new anticancer drugs by Chronotherapy – the results of which were bases for two clinical trials of the European Organisation for Research and Treatment of Cancer (EORTC).

From 2002-2006 she worked in the pharmaceutical company Sanofi-Aventis in Paris. As a Senior Scientist in the Experimental Therapeutics Section at the Department of Oncology, she focused on the preclinical assessment of the activity of new anti-cancer compounds. During this period she also participated in the discovery of several molecules that have been approved for commercialisation or are currently in clinical development.

In 2007 she joined the CNIO as Head of the Animal Pharmacology Section.

Summary

The Animal Pharmacology Section is dedicated to the *in vivo* exploration of the therapeutic potential of new molecules discovered by the CNIO Experimental Therapeutics Programme.

Using murine cancer models to provide information on the mechanism of action of compounds, the pharmacokinetic and pharmacodynamic relationships, and the assessment of safety and anti-tumour activity, we aim to identify and select the most effective molecules for potential clinical use.

Thus, we generate experimental data to support translational research in terms of biomarkers, clinical indications, administration schedule and combination treatment.

Main Objectives

- Evaluate the *in vivo* anti-tumour activity of new molecules discovered by the Experimental Therapeutics Programme
- Elucidate the mechanism of action of potential therapeutic agents
- Provide early pharmacokinetic and pharmacodynamic information





Post-doctoral fellow: David A. Cebrián. **Technicians:** Estela Casas and Patricia Villanueva (since April).

Highlights

The Animal Pharmacology Section evaluates and attempts to maximise the therapeutic potential of new compounds synthesised within the CNIO Experimental Therapeutics Programme.

During this year we continued to focus on the pharmacological evaluation of molecules derived from two current projects: the PI3K and PIM inhibitors. Twenty novel molecules generated from the PI3K project and 15 from the PIM1 project were evaluated *in vivo* – these molecules have demonstrated efficacy as well as a mechanism of action in tumour cells.

The molecules first underwent preclinical formulation assays to facilitate administering the test compound to mice by different routes. The aim is to provide an accurate *in vivo* exposure of the molecules, while preserving integrity in a physiologically compatible vehicle.

Tolerance studies determine the maximum tolerated dose or the optimal drug dosage, as well as the best administration schedule, thus providing information about the safety margin of the new molecules.

The Section is also responsible for the preliminary *in vivo* pharmacokinetic (PK) assays, aimed at studying the time-course of the drugs in the organism. Pharmacodynamics (PD) is the study of the biological effects of drugs. By integrating PK and PD it is possible to characterise the pharmacological effects of a molecule and relate these to its mechanism of action.

The *in vivo* mechanistic characterisation of our molecules allows us to analyse the modulation of different biomarkers in search of evidence of target or pathway inhibition in the whole animal, which normally translates into the biological effect.

Only the molecules that have successfully passed the previous assays are selected for the efficacy assessment. This step is carried out using appropriate tumour models (ectopic models, orthotopic tumours, genetically modified mice), selected according to tumour target expression, *in vitro* activity of the molecules, and clinical relevance.

Using several xenograft models we evaluated the antitumor activity of the top PI3K inhibitors as single agents or in combination with reference drugs (Figure). Our results show that our compounds present characteristics that justify their further development as anti-cancer drugs.

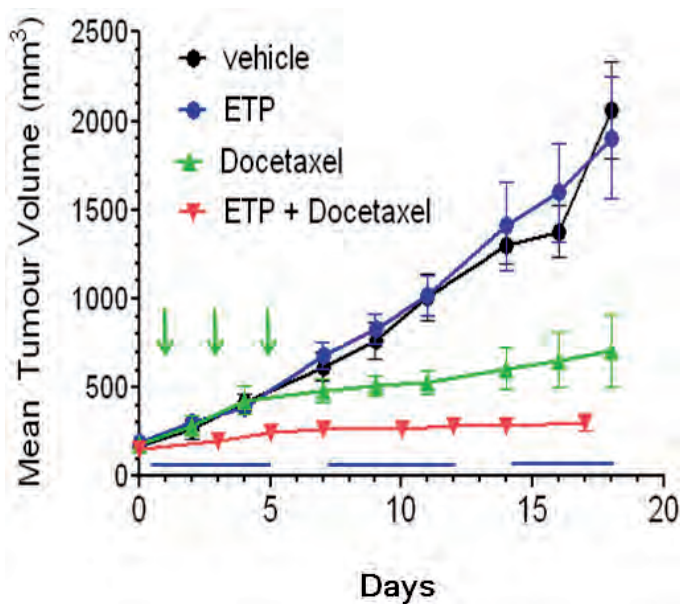


Figure: Antitumour activity of ETP-46321 in SK-OV-3 human ovarian cancer xenografts. Tumour-bearing mice were treated with ETP-46321 at 10 mg/kg (daily, 5 days a week for 4 weeks), Docetaxel at 10 mg/kg (every other day, three times), and the combination of ETP-46321 plus Docetaxel or vehicle alone. The combination had a significant effect on tumour growth, as compared to the single agents.