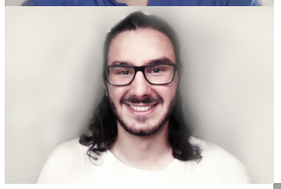
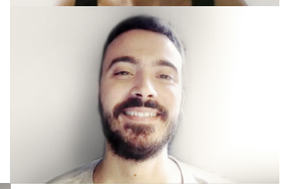
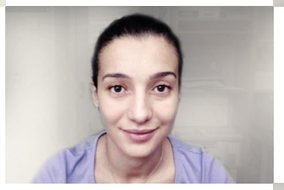
CELL DIVISION AND CANCER GROUP

Marcos Malumbres
Group Leader

Post-Doctoral Fellows
Begoña Hurtado (since July), María Salazar (until July), Carolina Villarroya






Graduate Students
Nuria García, José González, Luis Rodrigo López, Diego Martínez, Borja Pitarch (since November)

Technicians
Aicha El Bakkali, Ana María Revilla (September-November) (TS) *, Elisabet Zapatero (TS) *

Titulado Superior (Advanced Degree)

Students in Practice
Cristina del Álamo (until September) (*Universidad de Alcalá de Henares*, Spain), María Franco (since September) (*Universidad Carlos III de Madrid*, Spain), Jorge G. García (until June) (*Universidad Carlos III de Madrid*, Spain)

Visiting Scientist
Senn Wakahashi (Kobe University, Kobe, Japan)

OVERVIEW

The Cell Division and Cancer Group is interested in deciphering the mechanisms by which cell division and cell proliferation are regulated in mammalian cells. Our scientific interests are:

- → to understand the basic control mechanisms that regulate the cell division cycle.
- → to characterise the physiological and therapeutic consequences of cell cycle deregulation.
- → understanding self-renewal and pluripotency in stem cell biology and tumour development.
- → improving the use of old and new targets for cancer therapy.

As a final goal, we aim to generate information that will be useful for understanding basic mechanisms of cell function and to improve therapeutic strategies against cancer cell proliferation.

"Our group has proposed new therapeutic uses of CDK4/6 inhibitors in metastatic cancer, as well as new strategies to improve the function of pluripotent cells in regenerative medicine."

RESEARCH HIGHLIGHTS

Cell cycle inhibition in cancer in cancer therapy

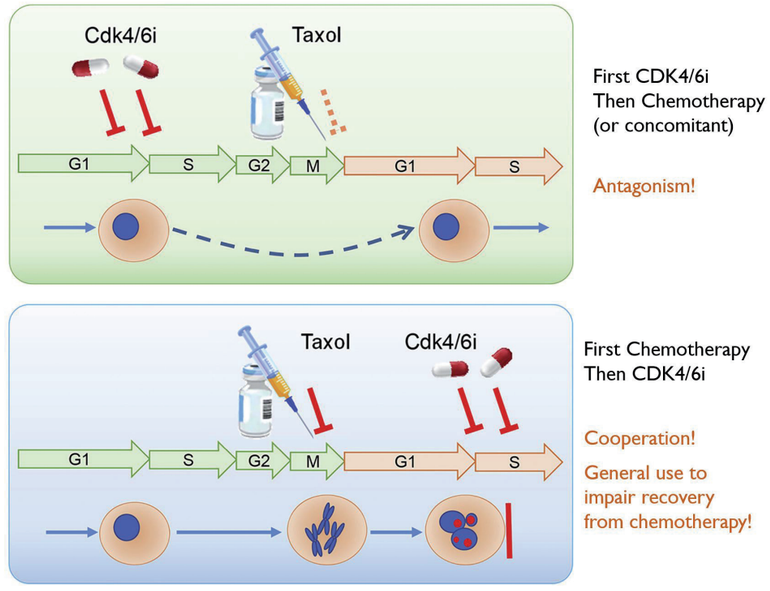
Inhibition of the cell cycle kinases CDK4 and CDK6 is currently part of the standard-of-care for the treatment of hormone receptor-positive, metastatic breast cancer. Inhibiting CDK4/6 activity is also considered an attractive therapeutic intervention for multiple other malignancies. However, it is generally assumed that these inhibitors should not be used in combination with classical chemotherapy, given that CDK4/6 inhibition arrests cells in G1, thereby protecting tumour cells from the cytotoxic effect of classical chemotherapy acting either in S-phase or mitosis in proliferating cells. Unfortunately, classical chemotherapy (DNA damaging agents, topoisomerase inhibitors, taxanes etc.) remains the treatment of choice for most patients with advanced disease. Using pancreatic adenocarcinoma (PDAC) as a model, we recently generated data suggesting that, both *in vitro* and *in vivo*, applying CDK4/6 inhibitors right after taxanes strongly cooperates to prevent tumour cell proliferation (FIGURE 1). We also demonstrated that the mechanism behind these observations is different from the classical model in which CDK4/6 are required for S-phase entry. We described that CDK4/6 activity is required for homologous recombination and DNA repair, and the recovery from the chromosomal damage imposed by taxanes or DNA damaging agents. This mechanism immediately suggests that CDK4/6 inhibitors could be efficiently used after a variety of classical chemotherapies, including nucleotide analogues, topoisomerase poisons and other DNA damaging agents, microtubule poisons, targeted anti-mitotic therapies, etc., as well as radiation. These results may have a major impact on the application of cell cycle inhibitors in the clinic in a variety of tumour types, and we are currently evaluating possible scenarios to move this strategy into clinical trials in breast cancer patients.

Improving the use of pluripotent cells in regenerative medicine

How pluripotent cells control their self-renewal and differentiation potential is becoming a major research topic in our laboratory. Our recent work suggests that a microRNA expressed in early development, miR-203, is able to induce naive pluripotency in both murine and human induced pluripotent cells (iPSC) and embryonic stem cells (ESC), thereby enhancing the potential of these cells *in vitro* and *in vivo*. Mechanistically, this effect is mediated through the repression of *de novo* DNA methyltransferases Dnmt3a and Dnmt3b and, global, but transient, genome demethylation. Application of miR-203 to iPSCs or ESCs mediates the resetting of the epigenetic memory and improves the developmental potential of these cells in multiple assays, including generating or live mice, complementation of tetraploid embryos, or interspecies assays in which human pluripotent cells are aggregated into mouse embryos. Exposure to miR-203 enhances the differentiation of mesenchymal cells from pluripotent cells *in vitro*, and improves the recovery from heart injuries in a model of cardiac infarctions in mice. These findings may have important potential implications in regenerative medicine that we plan to study in the upcoming years.

Finally, we are using a variety of genetically-modified mice and iPS/ES cells with specific mutations in cell cycle regulators to understand the basic mechanisms of control of cell cycle progression and self-renewal in pluripotent cells. Our preliminary data suggest interesting connections between cell cycle kinases and phosphatases, the developmental potential of neural progenitors, and the generation of developmental syndromes with defects in the nervous system, including primary microcephaly, a developmental defect resulting in smaller brain at birth. The molecular connections between centrosome dynamics, cell cycle regulation, and cell fate in neural progenitors are currently under analysis in these models. ■

FIGURE 1 A new strategy for the use of CDK4/6 inhibitors (CDK4/6i) in cancer therapy. It is well established that CDK4/6i impair entry into the cell cycle, thus antagonising the cytotoxic effect of classical chemotherapy (upper panel). However, our recent data suggest the sequential use of CDK4/6i "after" chemotherapy (bottom), thereby preventing DNA repair and recovery from the cytotoxic effect of many drugs that are the standard-of-care in a wide variety of metastatic cancers.



PUBLICATIONS

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